CUK-H06241-56-P25321

BJS

ISSN 0007-1323

British Journal of SURGERY

Volume 89
Number 9
September 2002

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The *BJS* ISSN 0007-1323

Published on behalf of the BJS Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
The Editors, *BJS*, Blackwell Science Ltd, 25 John Street, London WC1N 2BS, UK. Tel: +44 (0) 207 404 1831; Fax: +44 (0) 207 404 1927.

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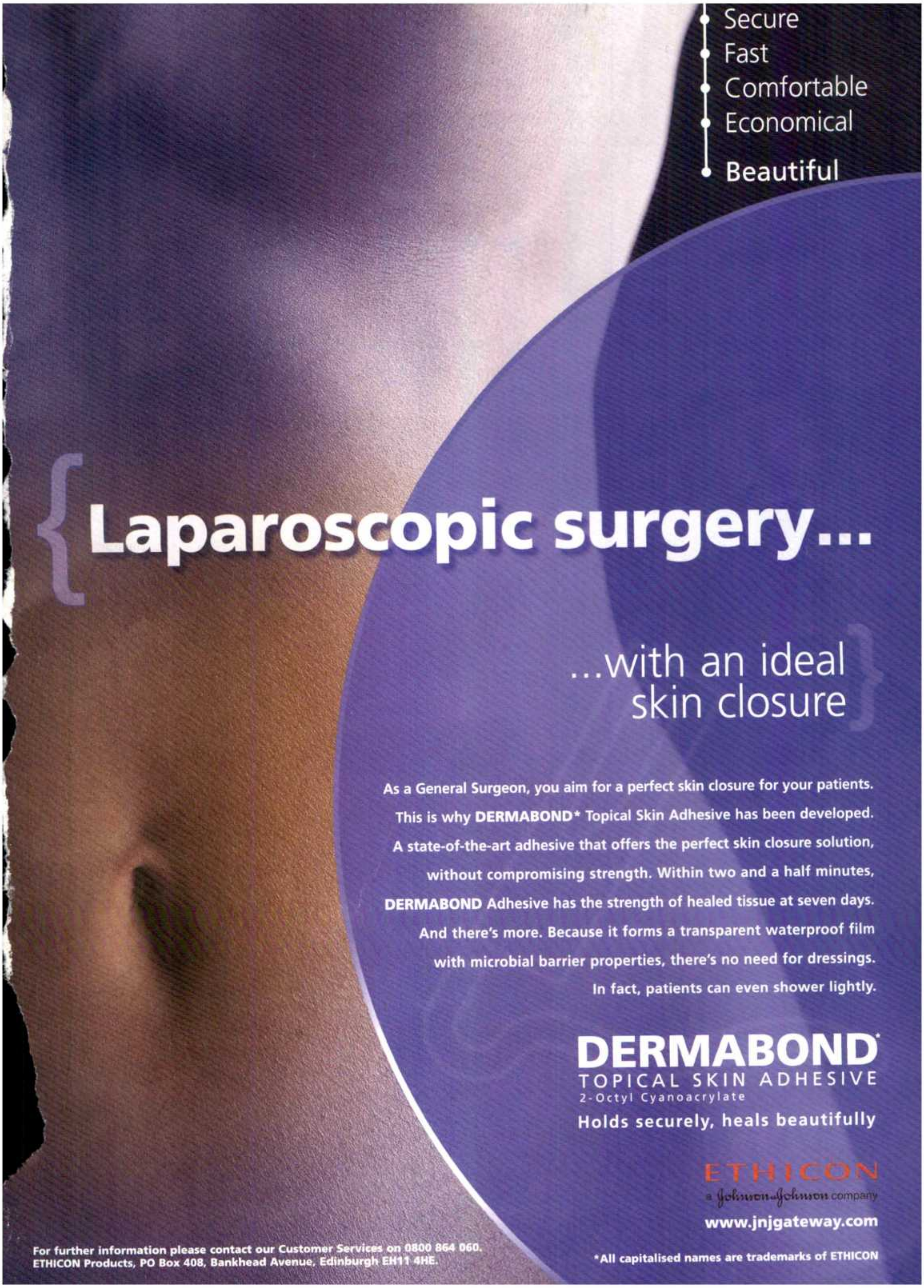

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used. For elderly patients weighing less tha
kg, initiate treatment with half the u
recommended dose and reduce the maxim
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hepatic impairment. In moderate hepa
impairment (Child-Pugh scale 7-9) use w
caution and at half the usual recommended d
and reduce the maximum daily dose to 40 mg.
recommended in severe hepatic impairment (Ch
Pugh scale >9). *Renal impairment:* Use caution in re
impairment or patients with fluid retention, howe
no dosage adjustment is usually necessary. *Childr*
Not recommended.
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substance or to any of the excipients. Patients w
have experienced bronchospasm, acute rhinitis, na
polyps, angioneurotic oedema, urticaria or allergic-ty
reactions after taking acetylsalicylic acid or NSAIDs
other cyclooxygenase-2 (COX-2) selective inhibitors.
the third trimester of pregnancy and breast-feeding. Se
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ulceration or gastro-intestinal bleeding. Inflammatory b
disease. Severe congestive heart failure.
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surgery. Caution should be used in coronary artery bypass g
surgery as a higher risk of certain adverse events is observed. Cau
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compromised cardiac or hepatic function (moderate hep
impairment). Dynastat may mask fever. Monitoring of incisions for
of infection following surgery is advised. Caution in those with histo
PUBs. Dynastat is not a substitute for acetylsalicylic acid (aspirin) in
prophylaxis. Caution when used concomitantly with warfarin. N
recommended in women attempting to conceive.
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increased risk of bleeding complications, however Dynastat does
affect pharmacodynamics of heparin. No effects observed
acetylsalicylic acid-mediated platelet aggregation. As for NS
may reduce the effect of diuretics, antihypertensives or increase
of acute renal insufficiency. Monitor renal function when c
administered with NSAIDs, tacrolimus or cyclosporin. May be
administered with opioid analgesics with a consequential reduct
the dose of morphine to achieve same level of ana
Pharmacokinetics: The dose of parecoxib sodium should be reduced wh
administered with fluconazole, a CYP2C9 inhibitor. No dosage adjustm
required when administered with ketaconazole (CYP3A4). Metabolism o
active moiety, valdecoxib may increase with enzyme inducers such
rifampicin, phenytoin, carbamazepine or dexamethasone. Caution should
observed with co-administration of medicines metabolised by CYP2D6 (e
flecainide, propafenone, metoprolol), or substrates of CYP2C19 (eg
phenytoin, diazepam, imipramine). Monitor for methotrexate-related toxicit
when given together. Lithium serum concentrations should also b
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anaesthetic agents nitrous oxide and isoflurane.
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postoperative anaemia, pharyngitis, respiratory insufficiency, pruritus, oligur
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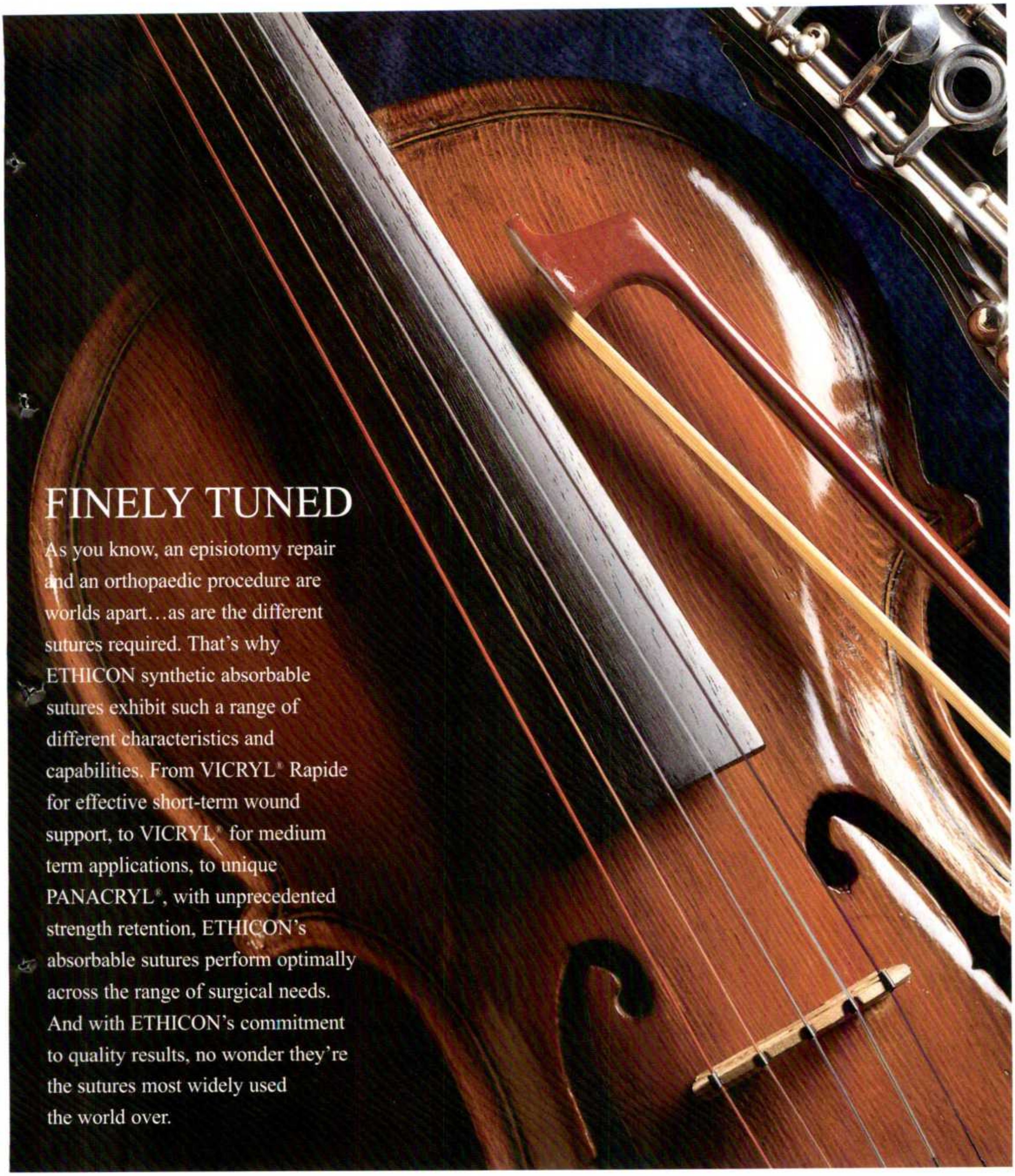

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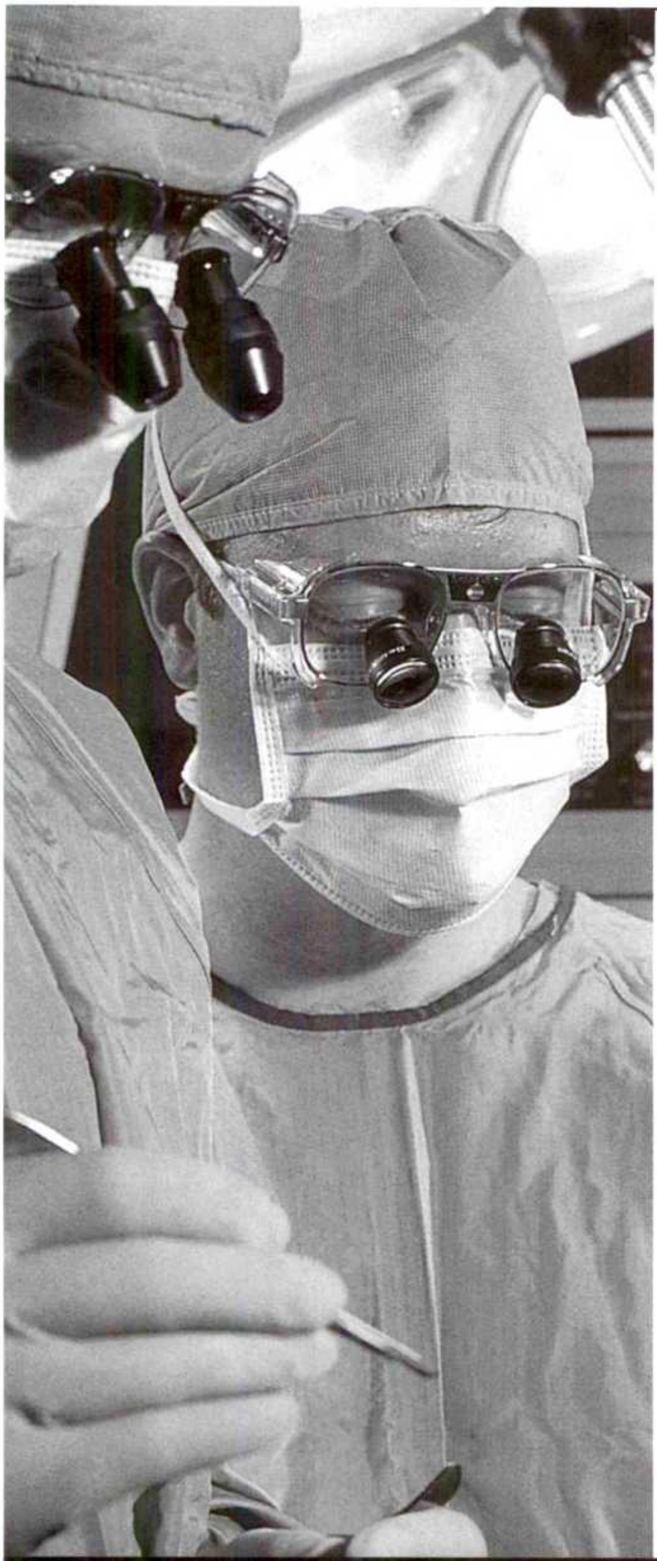

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Leading article

Lymph node dissection and medullary thyroid carcinoma

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Medullary thyroid carcinoma (MTC) differs fundamentally from thyrocyte carcinomas, not only in embryology and microscopic anatomy, but also in function, tumour biology, pathogenesis and genetics. Importantly, in contrast to thyrocyte carcinomas, MTC can be diagnosed at a preclinical stage by a specific secretory product, calcitonin. Furthermore, again in contrast to thyrocyte carcinomas, the hereditary variant of MTC can be identified unequivocally in about 95 per cent of patients; the *RET* proto-oncogene was identified by Mulligan and by Donis-Keller in 1993 as the susceptibility gene for hereditary MTC. A major disadvantage compared with differentiated thyroid carcinomas is the inability to treat MTC with radio-iodine. In addition, no multimodal treatment protocol has been proven effective in advanced and/or metastasizing MTC. Taken together, there is no currently available alternative to surgical treatment for both curative and palliative situations.

Total thyroidectomy

While some groups perform lobectomy in selected patients with genetically proven sporadic MTC[1], total thyroidectomy is generally accepted as the single essential element of primary surgical treatment for all forms and stages of MTC. The reasons are as follows. First, intraglandular lymphatic spread occurs in 10–20 per cent of patients with sporadic MTC. Second, the hereditary background is often unknown at the time of primary operation and may not even be detected in the case of rare mutations of the *RET* proto-oncogene. Third, radio-iodine treatment for microscopic intraglandular deposits is not effective in MTC. Despite the above, it must be conceded that there are no prospective studies of sporadic MTC that prove the outcome is better after total thyroidectomy than after unilateral lobectomy. On the other hand, no histological, biochemical or molecular markers currently exist to indicate those occasional patients who may benefit from non-total thyroidectomy. In hereditary MTC, because of the genetic alteration of the whole C-cell system, there can be no place for any resection less than total thyroidectomy.

Compartment-oriented microdissection

Compartment-oriented microdissection depends on certain features of lymph node colonization, which typically occurs in anatomically defined 'compartments' before the borders to the next lymph node compartment are crossed. This phenomenon occurs in several human cancers and is also evident in thyroid carcinoma, especially of the papillary and medullary types. Four locoregional lymph node compartments can be differentiated[2]: the central (first), ipsilateral–cervicolateral (second), contralateral–cervicolateral (third) and upper mediastinal (fourth) (*Fig. 1*). The definitive proof that these four compartments are really locoregional comes from the observation that not only papillary but also medullary carcinomas with metastases within these compartments are potentially curable. The superiority of this compartment classification compared with the Robbins and Union Internacional Contra la Cancrum (UICC) classifications of cervical lymph node groups has been proven by several international multicentre studies[3,4]. First, it reflects the biological principle of compartmental colonization within anatomically defined

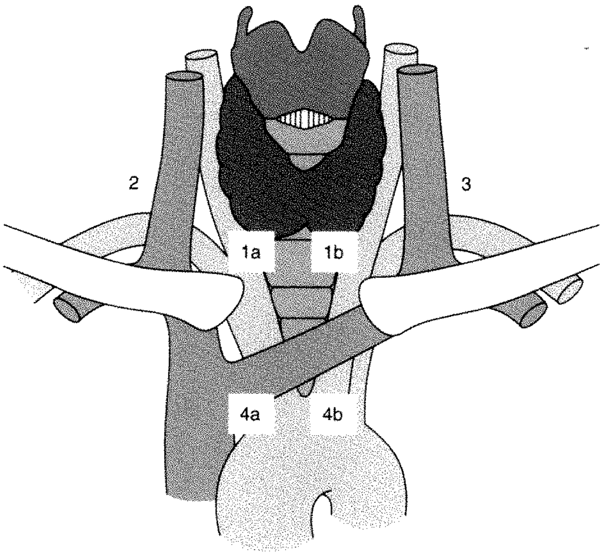

Fig. 1 Compartment classification: 1a, right cervicocentral; 1b, left cervicocentral; 2, right cervicolateral; 3, left cervicolateral; 4a, right upper mediastinal; 4b, left upper mediastinal

borders; second, it can be easily applied by different centres; third, it clearly differentiates the side of the neck; and fourth, it includes the infrabrachiocephalic upper mediastinum within the locoregional lymph node system.

Thyroid cancer needs its own lymph node staging system because tumour biology and locoregional metastatic routes differ completely from those of aerodigestive tumours of the neck. From pathoanatomical and pathohistological studies it can be concluded that lymph node metastases occur much more frequently in MTC than in papillary cancer (65 *versus* 47 per cent respectively). Moreover, compartmental tumour involvement of lymph nodes is greater in MTC than in papillary cancer. This means that in most cases of MTC more than one lymph node, or group of lymph nodes, is involved microscopically or even macroscopically.

The introduction of meticulous, compartment-oriented microdissection not only for primary but also for reoperative MTC surgery has been a great leap forward. It has resulted in a significantly improved rate of biochemical cure (normalization of stimulated calcitonin levels), from 30–50 per cent previously to 60–80 per cent for primary operation, and from 0–20 to 30–40 per cent for reoperation[2,7–9]. However, certain questions arise. How many compartments should be dissected in different tumour stages? How does compartmentectomy influence recurrence and survival in patients with local disease, with or without systemic disease?

Extent of lymph node dissection

There is ongoing controversy about what constitutes an adequate extent of node dissection for this rare tumour. This is complicated not only by problems arising from the tumour itself (often a chronic disease, even in the case of distant metastases), but also by the concept of 'the surgeon as a risk factor'; the latter is a training and experience issue. The central compartment is the first lymph node station in the overwhelming majority of thyroid cancers, including MTC. From local data on 339 patients with MTC treated from 1995 to 2001, it appears that only 15 per cent of node-positive MTC skips the central compartment and metastasizes directly to the ipsilateral cervicolateral nodes. However, at reoperation persistent lymph node metastases are often found in the central compartment (65 per cent of patients undergoing reoperation locally). The ipsilateral cervicolateral compartment is primarily involved as frequently as the central compartment (about 35 per cent for all tumour stages). Nevertheless, in reoperative cases persistent lymph node metastases are frequently found in the ipsilateral cervicolateral compartment (approximately 50 per cent of cases locally). The contralateral cervicolateral compartment is involved primarily in about 20 per cent of all patients with MTC; in the reoperative situation this value is only slightly higher than in the primary situation. The infrabrachiocephalic upper mediastinal compartment is involved in approximately 15–20 per cent of all patients with MTC, but in about half of those with pathological tumour (pT) stage 4 tumours (*Table 1*).

The chance of biochemical cure has been reported as correlating with the number of compartments and the number of lymph nodes involved; in one study no biochemical cure was associated with three or more involved compartments and ten or more involved lymph nodes[10]. To answer the question about which type of

Table 1 Locoregional lymph node involvement in medullary thyroid carcinoma

		No. of positive compartments resected*			
		Cervicocentral	Cervicolateral		Mediastinal
pT status	*n*		Ipsilateral	Contralateral	
Primary MTC					
pT1	35	5	4	0	0
pT2	16	5	6	3	2
pT3	3	0	0	0	0
pT4	14	12	13	8	7
Total	68	23 (34)	23 (34)	11 (16)	9 (13)
Reoperative MTC					
pT1	16	9	8	3	0
pT2	59	36	29	11	11
pT3	7	5	3	2	2
pT4	11	10	6	4	5
Total†	93	60 (65)	46 (49)	20 (22)	18 (19)

Values in parentheses are percentages. *Number per pathological tumour (pT) category by the respective pT population. †Excluding one pTx carcinoma. MTC, medullary thyroid carcinoma. Data from Machens *et al.*[6], with permission

Table 2 Surgical strategy for patients with medullary thyroid carcinoma

	Primary operation	Reoperation
No evidence or suspicion of distant metastases	TT, C1–3, C4 only in the case of nodal involvement	Completion operation according to extent recommended for primary operation
Distant micrometastases	TT, C1 + 2 or 3 (according to site of primary tumour), contralateral–cervicolateral and/or upper mediastinal compartmentectomy only in the case of nodal involvement	Completion operation according to extent recommended for primary operation
Distant macrometastases	TT plus selective removal of symptomatic lymph node metastases	Selective removal of symptomatic lymph node metastases

TT, total thyroidectomy; C1–4, compartments according to the compartment classification[2]

operation fits the majority of patients with MTC (those with an intrathyroidal MTC without distant macrometastases), the present author, like others[9], recommends total thyroidectomy with three-compartment lymphadenectomy (central plus bilateral cervicolateral) in primary as well as completion surgery (*Table 2*). Most difficult is the decision regarding the extent of operation in patients with locoregional and distant disease (proven or suspected). In the case of symptomatic locoregional disease and the presence or suspicion of distant micrometastases, the local pathology often plays the role of 'pacemaker' of the disease. For this reason the author recommends local tumour control by microdissection of the affected compartments. Only in the case of proven distant macrometastases would the extent of cervical reoperation be confined to the removal of symptomatic cervical nodes. Mediastinal lymph node dissection has a place only in curative interventions directed at proven metastases. Although this locoregional strategy should go along with an increased chance of biochemical cure, further long-term studies are necessary to establish its superiority in terms of disease-free survival.

The main problem today is to identify correctly patients with micrometastases by modern imaging techniques (or bone marrow analysis) and to differentiate between patients with progressive and those with stable disease. Ongoing research in this regard holds out hope of being able to modify the present concept of radical locoregional lymph node surgery in MTC. At present, the best way to cure the patient is early diagnosis in sporadic MTC, and prophylactic thyroidectomy in gene carriers of hereditary MTC[11].

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Staging of oesophageal adenocarcinoma

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Most patients now presenting with malignant dysphagia in the UK have adenocarcinomas involving the gastro-oesophageal junction (GOJ). Although they are often grouped together as one entity, evidence is emerging that these tumours differ biologically depending on their anatomical relationship to the GOJ[1]. Furthermore, there are important differences in clinical management that depend on their precise location. In the light of this, Siewert and colleagues[2] have proposed the following classification: type I carcinomas arise in the distal third of the oesophagus, usually in a segment of Barrett's oesophagus and may or may not directly involve the GOJ; type II straddle the GOJ and appear to arise at the true junction of the stomach and oesophagus; and type III are subcardial gastric cancers that have grown proximally to invade the GOJ.

Endoscopic ultrasonography has greatly improved our ability to stage junctional tumours before definitive therapy and, increasingly, this is influencing patient management[3]. In the current tumour node metastasis (TNM) staging system for oesophageal cancer (5th edition)[4], nodal metastases at the coeliac axis (station 9) are deemed M1a/b disease; by inference, patients so affected have stage IV disease and non-surgical palliation may be more appropriate than an attempt at cure by resection. However, in the TNM gastric cancer staging system the location of regional nodes below the diaphragm is irrelevant as it is the number of involved nodes that determines the N-stage. If Siewert's classification is applied, type I GOJ tumours are located in the tubular oesophagus and should, therefore, be staged using the oesophageal system, whereas type III tumours are gastric and so the gastric TNM staging system should be used. However, which system should be used for type II tumours? By definition they involve the oesophagus and stomach equally. Siewert and colleagues[2] believe that type II and III tumours should be treated in the same way, as the pattern of nodal spread and the survival rates following extended total D2 gastrectomy are similar. However, other groups have reached different conclusions, suggesting that type II tumours are more like type I and so should be treated as oesophageal cancers[5–7].

There is a pressing need for revision of the staging systems for junctional adenocarcinomas as the following case will illustrate. A patient with a type II GOJ T3 tumour from 38 to 42 cm is found on endoscopic ultrasonography to have a single malignant-looking paraoesophageal node at 38 cm. As this is not regarded as part of the regional lymphatic drainage of the stomach, it is deemed to be a distant metastasis. The tumour is therefore stage IV by the rules of gastric cancer staging, making palliation the principal aim. In contrast, if the oesophageal system were used this node would not be a distant metastasis and, as a T3 N1 tumour, the disease would be classified stage III and an attempt at cure would be justified.

The TNM staging systems for oesophageal and gastric cancer were both devised before the dramatic change in frequency distribution of upper gastrointestinal cancers. Oesophageal cancers were principally squamous lesions, arising in the proximal and middle thirds of the oesophagus; if these spread to the coeliac axis they were obviously incurable. Similarly, a typical distal gastric cancer was also beyond cure if it had metastasized to paraoesophageal nodes above the diaphragm. However, the regional lymphatic drainage of a tumour at the GOJ is both above and below the diaphragm[8], and the definition of a distant nodal metastasis should account for this. As highlighted by others[5], there is an urgent need for a review of the staging system for GOJ tumours in the light of these developments; it is time that an international panel met to discuss this.

The authors strongly support a new staging system for GOJ tumours. It should take into account the R-status of the resection by ensuring a standardized method of assessing radial resection margins and stratifying patients accordingly[9]. In addition, it should use a numbers-based assessment of positive nodes for N-staging instead of the current anatomical one, bringing it into line with the rules for staging gastric cancer. This would help with treatment planning, ensure that adequate numbers of lymph nodes were examined and improve the prognostic information derived from pathological staging. There is compelling evidence that the number of nodal metastases influences outcome in carcinoma of the oesophagus; proposals for new staging systems similar to the present one have been made on the basis of this evidence[10]. Once this new system has been applied successfully to type II tumours, whether or not it is applicable to other types of GOJ tumour should be assessed. In the meantime, clinicians must appreciate the importance of classifying junctional tumours as accurately as possible. Patients should be treated logically, based on the best information currently available.

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Surgical anatomy of segmental liver transplantation

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Background: The emergence of split and living donor liver transplantation has necessitated re-evaluation of liver anatomy in greater depth and from a different perspective than before. Early attempts at split liver transplantation were met with significant numbers of vascular and biliary complications. Technical innovations in this field have evolved largely by recognizing anatomical anomalies and variations at operation, and devising novel ways of dealing with them. This has led to increasing acceptance of these procedures and decreased morbidity and mortality rates, similar to those observed with whole liver transplantation.

Methods and results: The following review is based on clinical experience of more than 180 split and living related liver transplantations in adults and children, performed over a 7-year period from 1994 to 2001.

Conclusion: A comprehensive understanding and application of surgical anatomy of the liver is essential to improve and maintain the excellent results of segmental liver transplantation.

Paper accepted 10 April 2002

British Journal of Surgery 2002, **89**, 1078–1088

Introduction

Improved results of liver transplantation have led to a widening of the indications for treatment, which has in turn resulted in a worldwide shortage of donor liver grafts. Innovative techniques of split liver transplantation (SLT) and living donor liver transplantation (LDLT) have been designed to increase the source of available grafts for both adult and paediatric recipients[1,2]. Although an increase in the availability of cadaveric whole organs will help, SLT and LDLT will still be required, possibly more frequently than at present, to make up the shortfall. LDLT has the potential for causing morbidity in a perfectly healthy adult donor[3], and it is of paramount importance to minimize donor and recipient complications for the continuing success and application of such a technique. Most immediate postoperative biliary and vascular complications in donors and recipients can be attributed to technical problems and failure to recognize anomalous anatomy.

Although wide-ranging investigations such as intraoperative ultrasonography, angiography, computed tomography (CT) and magnetic resonance imaging are used routinely in living donors to map out the hepatic vascular and biliary anatomy[4,5], they are not performed routinely during a cadaveric split. Moreover, not all anomalies can be demonstrated with certainty by these investigations and some may be evident only when specifically sought. For these reasons it is essential that the transplant surgeon is well versed in normal liver anatomy and able to recognize the presence and implications of anatomical variations. This article discusses the normal and anomalous hepatic vascular and biliary anatomy and its application to SLT and LDLT based on our experience of more than 180 such procedures performed over a 7-year period from 1994 to 2001.

Hepatic veins and vena cava (*Fig. 1*)

The venous drainage of the liver comprises three main hepatic veins that drain into the suprahepatic part of the inferior vena cava, and a multitude of accessory hepatic veins that drain into the retrohepatic vena cava. The right hepatic vein, the longest vein in the liver, is single in about 94 per cent of cases and runs in the intersegmental plane between the anterior and posterior segments of the right lobe[6]. The main trunk is formed by the convergence of an anterior trunk situated in the right portal fissure, which drains mainly segments V and VI, and a posterior trunk that chiefly drains segment VII[7]. The middle hepatic vein courses along Cantlie's line in the principal portal fissure and forms a common trunk with the left hepatic vein in about 85 per cent of cases[6,7]. It drains the central sector of the liver, receiving constant tributaries from segment IV on the left, and from segments V and VIII on the right[8]. It is

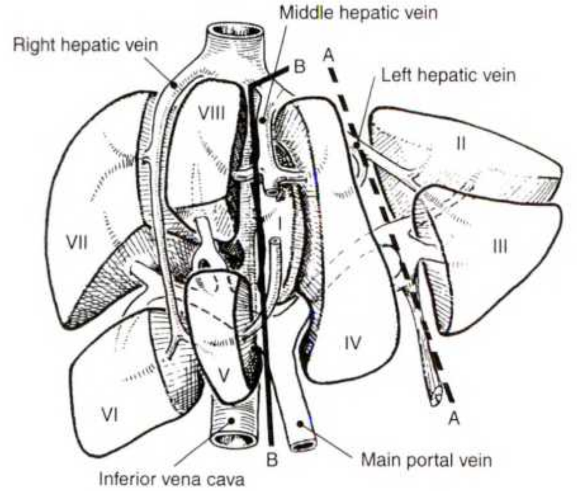

Fig. 1 Segmental anatomy of the liver demonstrating the pattern of hepatic venous drainage, ramifications of the portal venous system and the planes of liver splitting. A–A: plane of a conventional split into left lateral segment and (extended) right lobe. B–B: plane of a split into left lobe and right lobe

often the main vein draining the anterior segment of the right lobe.

The left hepatic vein arises from the confluence of a transverse vein, draining segment II, and a sagittal vein, draining segment III[7]. It occasionally receives a contribution from segment IV. The main trunk, in the majority of cases, forms a common channel with the middle hepatic vein and opens into the suprahepatic vena cava. Occasionally, it runs as an independent vein of the left lateral segment, draining separately from the middle hepatic vein.

Short accessory (dorsal) right hepatic veins, not to be mistaken for the caudate lobe veins, drain the dorsal sector of the liver (mainly segments VI and VII) and empty directly into the retrohepatic inferior vena cava on its right. The caudate lobe is drained predominantly on the left by a single vein in 50 per cent of livers and by two or three veins in the rest. In addition, there may be up to 20 small short venules attaching the caudate lobe to the retrohepatic inferior vena cava[9].

Variations and anomalies

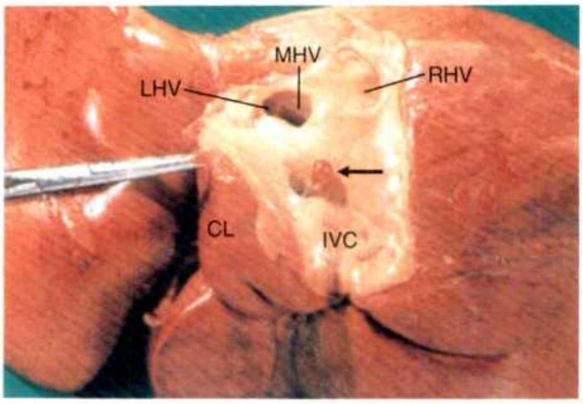

Fig. 2 Posterior surface of the liver with the inferior vena cava (IVC) split open, demonstrating a large inferior hepatic vein (with the red pin, arrowed) opening directly into the IVC, inferior to the opening of the main hepatic veins. RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; CL, caudate lobe

In 1981 Nakamura and Tsuzuki[6] made an extensive study of the patterns of the ramifications of the hepatic veins, and observed that the size of the main right hepatic vein seemed to determine the number of accessory hepatic veins and their diameters. In the presence of a large hepatic vein draining a wide area of the right lobe, only a small posterior vein drains a small area of the posterior sector of the right lobe, with occasional absence. If the main right hepatic vein is medium sized, a posterior or posteroinferior vein, 0·5–1 cm in diameter, drains the posteroinferior segment (segment VI) of the right lobe separately into the vena cava (*Fig. 2*). In just under a quarter of livers, however, the right hepatic vein is small and short, and drains only segment VII, while a large posterior or posteroinferior vein, up to 1·8 cm in diameter, drains the bulk of the posteroinferior area of the right lobe. In such circumstances the anterior segments can drain solely into the middle hepatic vein.

The middle and left hepatic veins form a common trunk in the majority of cases. In addition, small individual veins, draining segment III or the superior part of segment IV (segment IVa), may empty directly into the suprahepatic inferior vena cava close to the main left hepatic trunk, a feature usually absent on the right side[6]. The intersegmental area between segment IV and the left lateral segment forms a watershed between the drainage territories of the middle and left hepatic veins. This is drained in more than 60 per cent of livers by a tributary of the left hepatic vein that runs across the falciform ligament, and in up to 30 per cent of cases equally between tributaries of the left and the middle veins. In less than 10 per cent the entire segment III is drained by its vein, which joins the middle hepatic vein instead of uniting with the segment II vein[6].

Implications

The commonest form of liver splitting involves division of the liver into a left lateral segment, based on the left hepatic

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vein, and a extended right lobe, based on the middle and right hepatic veins[10]. The line of splitting passes through the watershed zone, and tributaries of the left and middle hepatic veins draining this zone are invariably encountered. These can be ligated without compromising the outflow of the left lateral segment or segment IV. However, care is required when dealing with a segment III vein draining into the middle hepatic vein. After parenchymal division, it may not be possible to reconstruct the outflow of the segment III and left hepatic veins into a single opening if their orifices are wide apart, and both may need to be implanted separately on to the recipient inferior vena cava. A similar problem may be encountered when a liver is being reduced, rather than split, down to a left lateral segment. Unexpected bleeding may occur during an *in situ* split or left lateral segment living donation when a large tributary of the left hepatic vein, draining part of segment IV, runs across the falciform ligament[6]. The presence of a transverse segment II vein permits resection of that segment to reduce a left lateral segment graft down to a 'monosegment' for transplantation in a very small baby[11], thereby overcoming a size discrepancy between donor and recipient of up to 15 : 1.

Differences in the pattern of drainage of the left hepatic venous system in the donor and recipient may cause anastomotic misalignment after implantation of the left lateral segment graft, leading to outflow obstruction. An adequate outflow is of vital importance for cut-surface haemostasis and optimal graft function. The triangulation technique for hepatic venous anastomosis has helped to counter this potential problem[12]. Intraoperative Doppler ultrasonography after liver reperfusion is useful in assessing the adequacy of vascular inflow and outflow, and helps to determine the best position in which to anchor the graft[13].

Regular use of SLT and LDLT for paediatric liver transplantation in an increasing number of centres has reduced pressure on waiting lists, and focus has returned to adult waiting times and organ shortage. Techniques are now evolving to split the liver into right and left lobe grafts for two adults[14]. The plane of dissection lies to the right of the middle hepatic vein to create two grafts of adequate and approximately equal mass for two adult recipients. This interrupts the venous outflow of segments V and VIII, which may cause congestion and troublesome bleeding from the cut surface of the right lobe after reperfusion; it may also compromise the functional volume of the right lobe graft. While the inferior vena cava can be allocated to either lobe, it is preferable to keep it with the right lobe in the presence of large accessory right hepatic veins. Alternative approaches include opening the inferior vena cava longitudinally to take a patch containing all tributary veins, and performing a cavocavoplasty in the recipient[15].

Procurement of a right lobe living donor graft may also be complicated by similar problems. It is helpful to map out the intrahepatic course of hepatic veins by intraoperative ultrasonography[7], especially that of the middle hepatic and accessory right hepatic veins in a right lobe donation. The presence of a 1-cm extrahepatic right hepatic vein cuff is helpful for a right lobe living donor harvest because of the ease of dissection and graft implantation on to the recipient inferior vena cava. If large accessory right hepatic veins are encountered, they must be implanted separately on to the recipient inferior vena cava. Extended right lobe living donation is practised relatively infrequently for fear of leaving behind insufficient liver mass in the donor. This can be further confounded by inadvertent damage or torsion of the left hepatic vein at donor operation, especially when the middle hepatic vein forms a common channel with the left hepatic vein.

The anatomy of the middle hepatic vein holds the key to right lobe living donation. In about 10 per cent of cases, when the right hepatic vein is of a small calibre, the middle hepatic vein can provide the sole drainage of the anterior segments of the right lobe. This has been considered to be a contraindication to right lobe donation[16]. Congestion of the anterior segments of the right lobe invariably occurs after parenchymal transection. However, it has been found that these segments develop ischaemia after reperfusion, rather than congestion[17]. This should be of no long-term consequence in the presence of an adequate vascular inflow and outflow, and a satisfactorily functioning liver mass.

Finally, congenital absence of the inferior vena cava in the recipient, as seen in syndromic biliary atresia, presents unique challenges in paediatric liver transplantation. In exceptional situations, a new vena cava may be reconstructed using a cadaveric iliac vein[18].

Portal vein (*Fig. 1*)

The portal vein divides at the hepatic hilum into right and left pedicles on which the right and the left lobes of the liver respectively are based. A theoretical plane, the main portal fissure, separates the two lobes[7]. The right portal vein, the shorter of the two, lies anterior to the caudate process and enters the liver through the hilar plate to divide into anterior and posterior branches. The anterior branch curves forward, lies in a vertical plane, and divides into ascending and descending branches for segments VIII and V respectively. The posterior branch curves posterolaterally, lying in a horizontal plane, and divides similarly for segments VII and VI respectively[8]. The left portal vein is much longer than the right and its course consists of two parts: a transverse part 3–5-cm long in the hilum, and a part that curves anteriorly and to the left as an arch towards the base of the umbilical fissure where it is joined anteriorly by the round ligament. The anatomy of the left portal venous system is remarkably constant. The segment II vein is usually solitary, whereas segment III can have up to three veins[8]. The arch then curves forward and distributes a varying number of ascending and descending branches to segment IV, which lie between the falciform ligament and the main portal fissure. The caudate lobe is most commonly vascularized by the left branch of the portal vein and only occasionally by the right[7].

Variations and anomalies

The right portal vein has more variations. A trifurcation of the main portal vein occurs in 10–15 per cent of cases, where the right portal vein immediately divides into two sectoral branches (*Fig. 3*). Occasionally one of the sectoral veins, usually the one supplying the right anterior segments V and VIII, comes from the left portal vein a short distance into its course (*Fig. 4a*). A third variation is the caudal shift of the right posterior segments resulting in the right posterior portal vein arising directly from the main portal vein, before its bifurcation[7] (*Fig. 4b*). In all of these circumstances the transverse portion of the left portal vein is usually shorter than normal. Finally, the left portal vein may rarely be absent (*Fig. 5*). In such cases the main portal trunk is undivided as it enters the liver, gives off its right segmental branches and then turns left, crossing the umbilical fissure intraparenchymally as the left portal vein and then supplies branches to the left lobe segments.

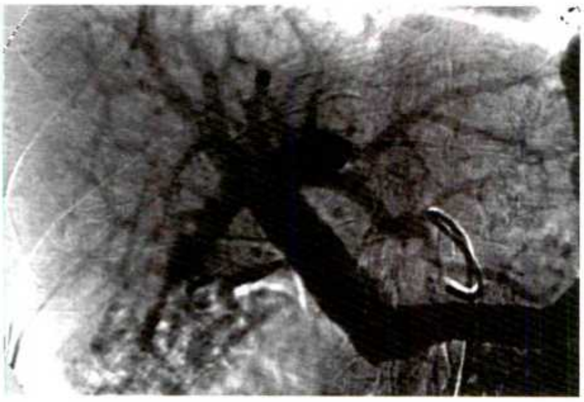

Fig. 3 Portal phase of an arterioportogram showing trifurcation of the main portal trunk

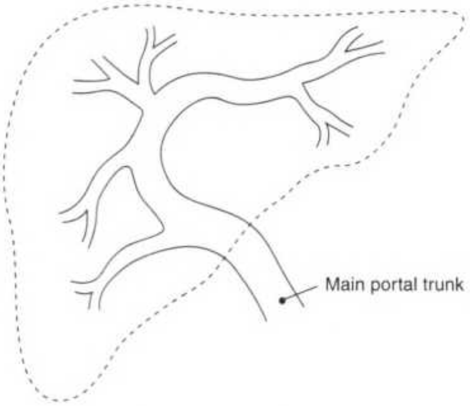

Fig. 5 Non-division of the portal trunk with absence of a separate left main portal vein

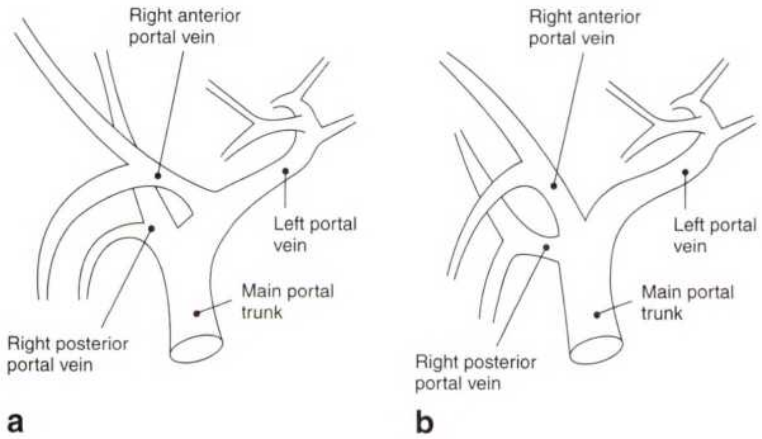
Right anterior portal vein
Left portal vein
Main portal trunk
Right posterior portal vein
a
Right anterior portal vein
Left portal vein
Main portal trunk
Right posterior portal vein
b

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Fig. 4 Anomalies of the portal venous system bifurcation. **a** Right anterior portal vein draining into the left main portal trunk. **b** Right posterior portal vein branching out from the main portal trunk before its bifurcation

Implications

Splitting a liver into a left lateral segment and a right lobe invariably interrupts the portal inflow into segment IV with resultant ischaemia (see *Fig. 7b*). Whether or not that segment needs to be discarded after a standard split remains a matter of debate. Transecting a right sectoral vein arising from the left portal vein can partially devascularize the anterior segments of the right lobe, if the liver is being split into a right and a left lobe for two adults, or if a right lobe is being harvested from a living donor. This is usually not of clinical significance and should not be considered a contraindication to these procedures. The presence of a portal vein undivided at the hilum is an absolute contraindication to living related right lobe donation or SLT. However, this problem has been overcome in reduced left lateral segment harvesting by gaining intraparenchymal access to the portal vein as it courses into the left lobe, and then using a vein graft anastomosed end to side of the portal vein[19].

Failure to recognize a portal vein trifurcation may jeopardize the middle branch, which usually runs as one of the two sectoral branches of the right portal vein. It may then compromise portal flow into the anterior or posterior segments of the right lobe. However, a trifurcation, even when demonstrated before operation, is not necessarily a contraindication to right lobe living donation. The portal vein needs to be divided just to the right of the trifurcation, which then leaves the right lobe with two separate portal branches. As these are close to one another, a back-table venoplasty can be performed to create a single lumen. Alternatively, both branches can be anastomosed either separately on to the recipient portal bifurcation, with or without the use of interposition grafts[20], or to the recipient main portal vein with an interposition Y graft[21]. The shortness of the transverse portion of the left portal vein in cases of a trifurcation may pose difficulties during retrieval and implantation of the left lateral segment graft; it is usually necessary to divide segment I branches in the donor to gain adequate length for anastomosis.

Arterial anatomy

The common hepatic artery, a branch of the coeliac trunk, but occasionally of the superior mesenteric pedicle, supplies the liver with arterial blood through its right and left hepatic branches. However, the origins of these two vessels are subject to considerable variation, the commonest being a left hepatic branch from the left gastric artery (*Fig. 6*) and a right hepatic branch from the superior mesenteric artery[22]. Accessory hepatic arteries from the left gastric and superior mesenteric vessels are frequently present and these may be 'replaced' rather than true accessory arteries[22]. The common hepatic artery may divide into its terminal branches anywhere between its origin and the hilum of the liver. The division usually takes place to the left of the hilum, resulting in a slightly longer right artery[8]. The right hepatic artery then courses laterally, posterior to the common bile duct and right hepatic duct, and enters the liver parenchyma. The left hepatic artery courses along the inferior aspect of the left lobe, with the left hepatic duct and left portal vein, for a varying distance before entering the left lobe at the level of the umbilical fissure. The caudate lobe and caudate process receive separate branches from the right and left hepatic arteries in what has been described as an 'arcade' or 'tree' pattern[23].

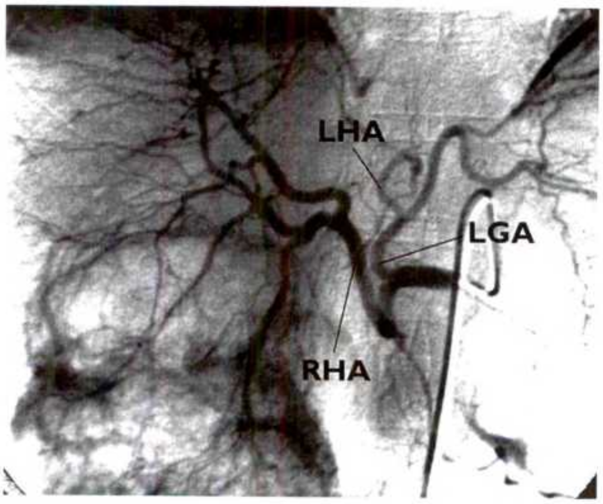
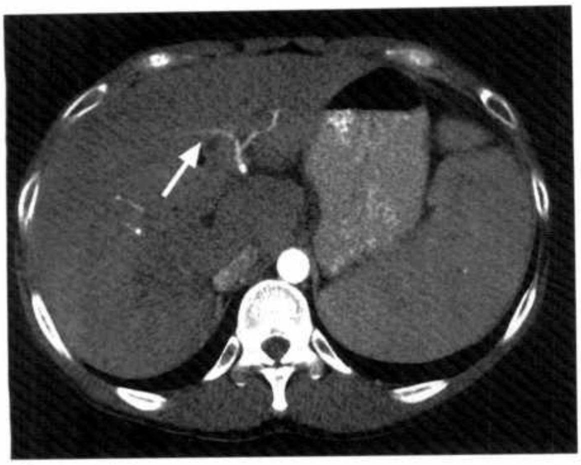


Fig. 6 Coeliac angiogram demonstrating the origin of a 'replaced' left hepatic artery (LHA) from the left gastric artery (LGA). RHA, right hepatic artery

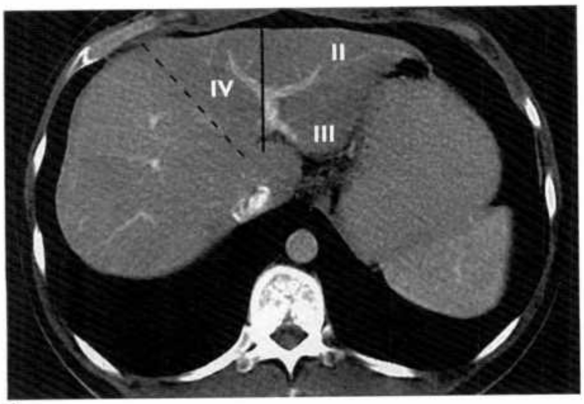
Variations and anomalies

The anomalies of the arterial system rival those of the biliary tract but, unlike biliary anomalies, they are important in both segmental and whole liver transplantation. Extrahepatic anomalies are recognized readily at standard multiorgan retrieval, and arterial reconstruction is a relatively routine procedure although it increases the likelihood of complications. Arterial anomalies in the donor and recipient may occur and influence implantation. Approximately 55 per cent of the population has conventional arterial anatomy[22].

The commonest variation is a left hepatic artery arising from the left gastric artery; this occurs in approximately 25 per cent of cases. This accessory left hepatic artery may provide the whole inflow to the left lateral segment in nearly



a Arterial phase



b Venous phase

Fig. 7 **a** Arterial phase of a spiral computed tomogram showing segment IV artery (arrow) arising from the left hepatic artery. **b** Venous phase of a spiral computed tomogram showing portal inflow to segment IV from the left portal vein, which is interrupted during a standard left lateral segment split. Solid line depicts the plane of a conventional left lateral segment split; interrupted line indicates the plane of a left lobe–right lobe split

half of these. An accessory right hepatic artery from the superior mesenteric is present in about 17 per cent of cases, and in 12 per cent it provides the entire supply of the right lobe. The hepatic arterial trunk arises in about 2·5 per cent of people wholly from the superior mesenteric artery and, more rarely, from the left gastric artery[21] or the aorta. Of importance in the latter cases is the higher prevalence of anomalous hilar anatomy than is observed with conventional anatomy.

Implications

It is well known that each artery, whether accessory or replaced, must be preserved because it has its specific terrain of blood supply; each artery is, as a rule, an end artery with no anastomosis inside the liver[22]. Hepatic arterial reconstruction is frequently necessary and is much more difficult during LDLT or SLT, as opposed to whole organ transplantation, because the graft arteries are smaller and shorter and, at times, multiple arteries need to be taken with the graft to enable left lateral segment donation without damaging the right hepatic artery of the donor[24]. Dual blood supply to the left lateral segment has been considered a relative contraindication for living donation[25], but many groups have overcome this by the routine use of microsurgical arterial reconstruction[4]. A selective policy, avoiding more complex arterial reconstructions, is feasible in countries with cadaveric donation.

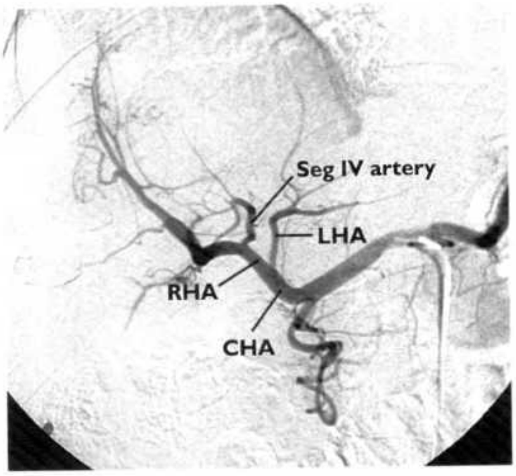


Fig. 8 Coeliac angiogram showing segment IV artery arising from a larger right hepatic artery (RHA). LHA, left hepatic artery; CHA, common hepatic artery

Although segment IV usually receives its supply from the left hepatic artery (*Fig. 7a*), it is not uncommon for the entire supply to come from a branch of the right hepatic artery (*Fig. 8*) which traverses Cantlie's line[23]. When significant in size, this vessel also supplies small branches to segments II and III. Non-recognition of this anomaly may result in the blood supply to segment IV being compromised in a right lobe living donor, with or without an associated bile leak. As these vessels may have an extrahepatic course at the hilum, careful identification and preservation of this vessel is possible by dividing the right hepatic artery beyond the origin of the segment IV artery. One must, however, avoid skeletonizing the bile ducts at the hilum.

Rare anomalies include an accessory artery to the left lobe segment from the common hepatic artery before its bifurcation[23]. A right accessory arising from the left hepatic artery and running behind the portal vein has been described[26], and is at risk during a left lobe living harvest.

A curious anomaly that may preclude a living right lobe donation has recently been described by Renz *et al.*[27] wherein an accessory right hepatic artery arises from the common hepatic artery and passes inferolaterally to supply the inferior portions of segments V and VI.

Most of the significant arterial anomalies should be visualized in the living donor by preoperative CT or magnetic resonance angiography, but these tests are not performed routinely for a cadaveric split. As the vascular supply of segment IV is so variable, it has been proposed that a cadaveric split be limited to segments II and III[23]. The presence near the hilum of a vascular plexus supplying the extrahepatic and intrahepatic biliary radicals always needs to be kept in mind with a view to minimizing hilar dissection, thereby reducing the incidence of postoperative ischaemic biliary stricture.

Biliary anatomy

Interesting challenges can be presented by variations in the biliary anatomy at the hilum and the mode of confluence of lobar and sectoral ducts. So many variations of the biliary tree exist that the 'normal' anatomy is present in only about 50 per cent of people[28]. Usually, a short vertical right hepatic duct and a longer horizontal left hepatic duct join at the hilum to form the common hepatic duct. The right duct is formed by the fusion of the right anterior and posterior sectoral ducts at a variable point in its intrahepatic course. These individual ducts, in turn, course along the vascular pedicles, draining the anterior (V and VIII) and posterior (VI and VII) segments of the right lobe of the liver. The left duct is formed by fusion of segment II and III ducts. The segment IV duct is more variable, but most commonly drains into the left hepatic duct.

Knowledge of the blood supply of the extrahepatic biliary apparatus is important when performing hilar dissections (*Fig. 9*). The arterial supply to the supraduodenal bile duct is predominantly axial (98 per cent related to vessels at its upper and lower ends). On average, eight small vessels, 0·3 mm in diameter, supply the supraduodenal bile duct. The most consistent and functionally important of these vessels are the 3 and 9 o'clock arteries that run along the lateral borders of the common bile duct. Approximately 60 per cent of the vessels that supply the supraduodenal duct run upwards from the gastroduodenal arcade below, while 38 per cent run down, mainly from the right hepatic artery. The remaining 2 per cent is a non-axial supply arising from the common hepatic artery. The arterial inflow to this vascular plexus arises mostly from the retroduodenal artery below and the right hepatic artery above. A vascular plexus composed of branches arising directly from the right, left and accessory hepatic arteries, if present, surrounds the hilar and intrahepatic bile ducts. This plexus is in direct continuity with that which surrounds the common hepatic and common bile duct. The plexus surrounding the intrahepatic bile ducts is closely associated with the arterial supply of the caudate lobe[23,29].

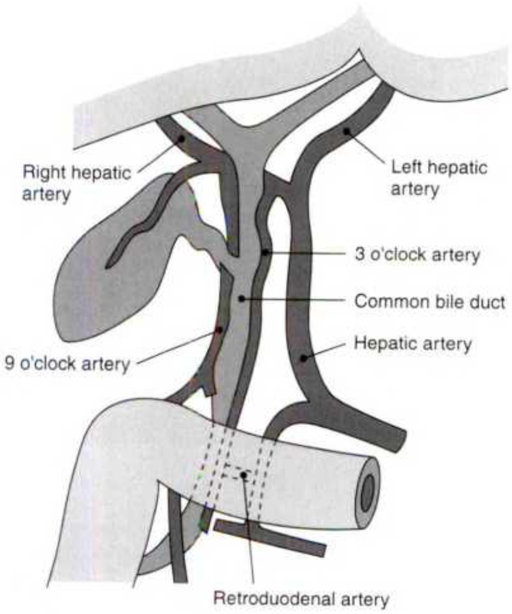


Fig. 9 Arterial supply of the extrahepatic biliary tree

Variations and anomalies (*Fig. 10*)

Smadja and Blumgart[28] have classified these variations into six main types. In type A (57 per cent) the anatomy is normal. In type B (12 per cent) there is a trifurcation of the common bile duct into right anterior, right posterior and the left hepatic duct, with an absence of a demonstrable length of the right hepatic duct. In type C (20 per cent) there is an aberrant drainage of the right segmental ducts into the common hepatic duct (*Fig. 11*). In type D (6 per cent) there is an aberrant drainage of the right segmental ducts into the left hepatic duct. The right posterior duct is more commonly aberrant than the right anterior duct in both type C and type D. In type E (3 per cent) there is absence of hepatic duct confluence, there being convergence of two or more ducts from either lobe to form the common hepatic duct. Finally, in type F (2 per cent) there is an absence of the right hepatic duct with ectopic drainage of right posterior duct into the cystic duct.

Implications

The incidence of biliary complications is greater after split[10] and living donor transplantation than after whole

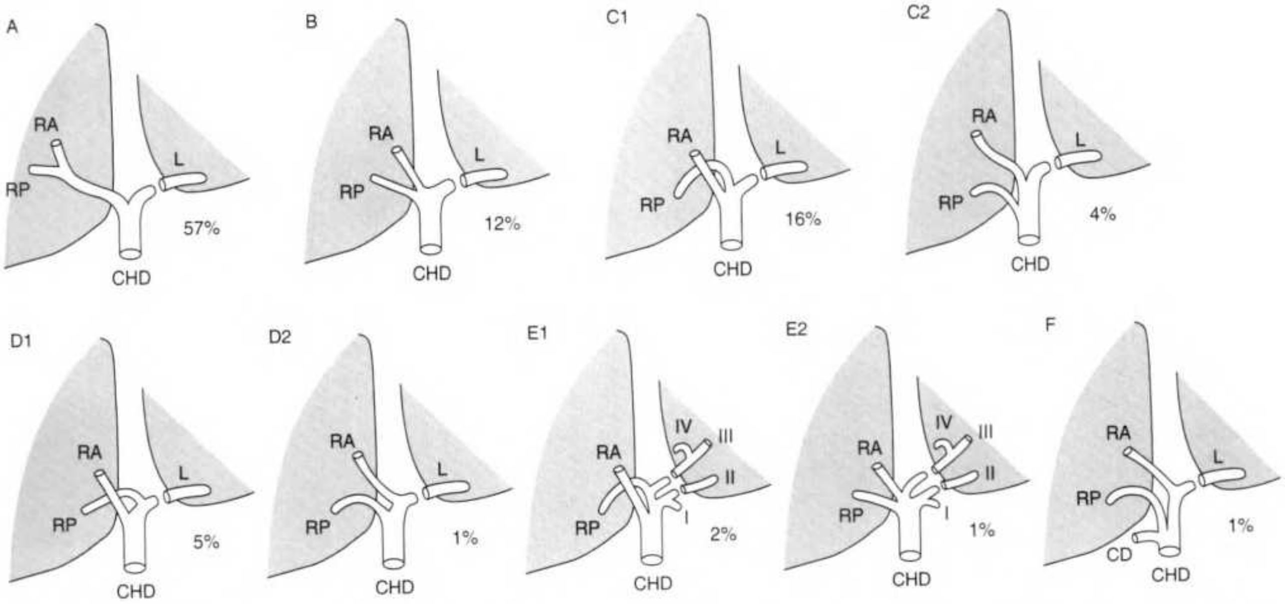


Fig. 10 Variations and anomalies of the biliary tree in relation to split and living related liver transplantation. CHD, common hepatic duct; RA, right anterior hepatic duct; RP, right posterior hepatic duct; L, left hepatic duct; CD, cystic duct

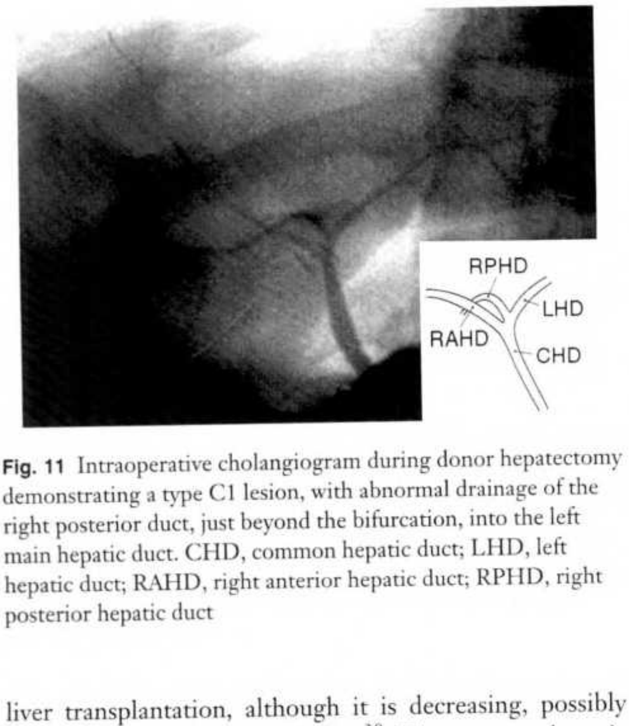


Fig. 11 Intraoperative cholangiogram during donor hepatectomy demonstrating a type C1 lesion, with abnormal drainage of the right posterior duct, just beyond the bifurcation, into the left main hepatic duct. CHD, common hepatic duct; LHD, left hepatic duct; RAHD, right anterior hepatic duct; RPHD, right posterior hepatic duct

liver transplantation, although it is decreasing, possibly with the advent of *in situ* splitting[30]. The common hepatic duct is invariably allocated to the right lobe of a split as the only source of its blood supply is superior, from the right hepatic arterial plexus. With right lobe living donation, biliary complications are more common because of the anomalies of right hepatic duct anatomy[31].

In about 69 per cent of cases with type A and B variations there should be no specific problem for either a conventional split or a left lateral segment living donation, or for a central split, especially if there is a significant length of the main left hepatic duct. Type C and D anomalies, associated with aberrant drainage of the right sectoral ducts, are present in 26 per cent of cases; the right posterior duct is anomalous in 21 per cent and the right anterior duct in 5 per cent. It could be argued that in type C, and in some cases of type D, anomaly there is actually a low division of the common bile duct into a smaller right hepatic and a larger left hepatic duct, rather than an abnormal insertion of a right sectoral duct into the common bile duct. The common implication in both these types is a greater risk of damage to the right sectoral ducts during a central split. Living donation, however, poses unique challenges. A right lobe retrieved from a living donor with a type C or D anomaly results in two separate ducts on its surface, whereas left lobe retrieval can frequently result in transection of one of the sectoral ducts of the liver remnant.

In type E anomalies, although the biliary anatomy is much more complex, a standard split does not compromise parenchymal biliary drainage but does leave two separate ducts on the cut surface of the left lateral segment. Renz *et al.*[32] reviewed the biliary anatomy of the left lateral segment by studying cadaveric dissections and corrosion casts. They noted a similar anatomy in about 10 per cent of cases, where there is no left lateral segment duct as the segment II and III ducts join close to the hepatic hilum. This, too, results in two separate ducts over the surface of the left lateral segment which must be anastomosed individually on to a Roux loop. In general, no attempt to obtain a single duct orifice in the graft should be made at the expense of compromising normal bile flow in the donor[20].

Notwithstanding these anatomical variations, the type of biliary anastomosis necessary in the recipient, and the incidence and types of biliary complications encountered after segmental liver transplantation, depend largely on the plane of dissection. A standard split frequently results in two separate ducts over the surface of the left lateral segment, as noted above; however, the chance of damaging an abnormally inserted right sectoral duct is less than that of a right lobe–left lobe split for two adults. A transected duct can be identified more readily at a living donation or an *in situ* split as a visible surface leak as opposed to an *ex situ* split. In a right lobe living donation the common bile duct must remain in the donor and the plane of dissection is more to the right than at a central split for two adults. Two or more ducts are frequently encountered over the cut surface of the right lobe, one of them being the more commonly aberrant right posterior duct, requiring a dual biliary anastomosis in the recipient.

Anomalous drainage of a segment IV duct into the right hepatic duct, if unrecognized during a right lobe living donor harvest, may lead to bile leaks in both the donor and recipient, or in both recipients if the liver is split centrally for two adults. These leaks generally settle spontaneously in the donor, particularly if the duct is small, and also in the recipient if the biliary anastomosis is widely patent. Segment IV leaks can also occur during a left lateral split, or living donation in the presence of normal anatomy, if the distal end of the segment IV duct fails to be ligated (*Fig. 12*). These leaks may resolve spontaneously in the donor as a result of atrophy of segment IV associated with vascular compromise. The incidence of such accidents during conventional splitting or right lobe living donor harvest can be minimized by cutting the left hepatic duct as close to the parenchymal surface as possible, thereby dividing it distal to any anomalous right segmental ducts draining into the left duct.

It is imperative to minimize handling and dissection at the hilum, not only to prevent injury to anomalous ducts but also to preserve the underlying vascular plexus, which contributes to the blood supply of both intrahepatic and extrahepatic bile ducts. Delayed anastomotic and non-anastomotic strictures are well known in whole and segmental liver transplantation, and are frequently associated with unrecognized ischaemic injury to the bile ducts[33]. The hepatic duct confluence seems to be particularly vulnerable to such ischaemic-type strictures[34].

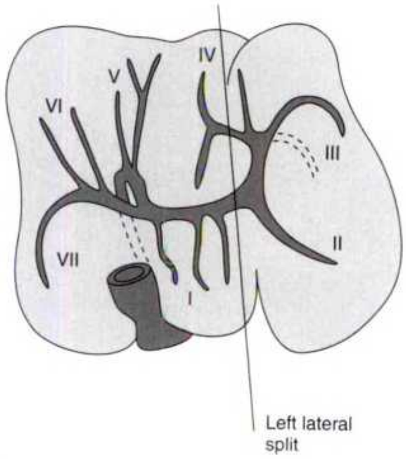


Fig. 12 Inferior view of the liver with projected biliary anatomy showing the line of a standard liver split, resulting in isolation of biliary drainage from segment IV

Preoperative magnetic resonance cholangiopancreatography and intraoperative cholangiography have the potential to identify anomalies and so minimize the incidence of postoperative bile leak and stricture. This is performed routinely in all right lobe living donations. Bench cholangiography is also useful in delineating abnormal anatomy, but is not practised universally. Gentle probing of the ducts with an atraumatic probe can yield vital information about anomalies. Flushing of the main ducts under low pressure with saline or a weak blue dye may identify leaks from the parenchymal surface.

With an indepth knowledge of biliary anatomy and performance of a careful hilar and parenchymal dissection, anomalies can be recognized and dealt with in over 95 per cent of cases, thereby obviating the need for routine bench cholangiography. However, the chances of injury to a right sectoral duct abnormally draining into the left duct are much greater when a liver is being split centrally for two adults, as opposed to a conventional right lobe–left lateral segment split, so bench cholangiography can be recommended as routine in such circumstances.

Conclusion

Postoperative problems, such as bile leaks, surface bleeding and vascular complications, have been significant in SLT and LDLT, especially in earlier series. Even today, biliary complications still occur in 20–25 per cent of SLT[35,36] and 15–30 per cent of LDLT[1,37,38] recipients. Moreover, biliary complications also occur in 5–10 per cent of donors for both adult-to-child and adult-to-adult living donation[3]. Vascular complications, such as arterial thrombosis and outflow obstruction, may lead to loss of valuable grafts. Long-term biliary and vascular complications both cause significant morbidity and mortality. Such complications must be minimized.

Worldwide acceptance of SLT and LDLT has required a revisiting of the complexities of the hepatic vascular and biliary anatomy to understand its application to these procedures. It is hoped that increasing experience, coupled with refinement of technique and a sound knowledge and application of anatomy, will lead to an improved outcome for patients undergoing segmental liver transplantation.

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Review

The mystery of liver regeneration

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Background: Partial hepatectomy is the strongest stimulator of hepatic regeneration. The process of initiation and the control of the final size of the regenerated liver have been the subject of research for many years. A better understanding of this process and the effect of disease may allow better selection of patients for partial hepatectomy. It may also allow an insight into the possible application of clinical stimulation of regeneration.
Methods: Data were reviewed from the published literature using the Medline database.
Results: Most knowledge comes from *in vitro* studies and the study of resection in the rat model. A variety of cytokines, hormones and growth factors are involved in regeneration but very few have been found capable of stimulating regeneration *in vitro*. The exact interactions are not known, but there is probably a cascade involving different factors at differing stages of regeneration.
Conclusion: Further *in vivo* research should allow greater understanding of liver regeneration, thereby providing a potential therapeutic tool in patients for whom regeneration has failed, or is likely to fail. Such research is also important in respect of liver support devices, which may inhibit liver regeneration by filtration of many of the factors involved.

Paper accepted 17 April 2002

British Journal of Surgery 2002, **89**, 1089–1095

Introduction

A fascinating aspect of the liver is its remarkable capacity to regenerate itself after injury. Even after major insult, such as surgical resection, it usually recovers sufficient function within a couple of weeks to be able to sustain life; fulminant hepatic failure or end-stage cirrhosis are exceptions[1]. The processes by which the liver accomplishes this feat are complex, and may depend on the mechanism of injury.

Regeneration is the ability to restore tissue mass and function after injury or partial resection. Most organs are incapable of increasing cell numbers after injury, although some may undergo cell hypertrophy. The liver, however, is able to re-establish its optimal volume in relation to body size after injury and cell loss through DNA synthesis and mitosis. It does not regenerate in the true sense, however, as in the case of reptiles that can regrow a limb or tail. After partial hepatectomy the resected liver lobe does not grow back; instead the residual tissue hypertrophies until the original mass has been restored. Once this has been attained, liver regeneration halts abruptly[2]. Interestingly, work on orthotopic partial liver transplantation in humans has revealed that the transplanted graft regenerates rapidly if it is small, while conversely it atrophies if it is too large for the recipient. Either way, an optimal liver-to-body mass ratio results[3,4].

The regenerative capacity of the liver is almost unlimited, as demonstrated by repeated liver resection in rats[5]. Under normal circumstances, the human liver initiates regeneration within 3 days and has reached its original size by 6 months[6,7], although some studies have shown full restoration at 3 months[7]. In most cases, liver function is restored to almost normal levels within 2–3 weeks after partial hepatectomy or in survivors of fulminant hepatic failure[7,8]. Bioartificial liver devices have been used to support patients with fulminant hepatic failure while the liver is in the process of regeneration. However, it is not known whether these devices actually affect the process of regeneration, as it is possible that the type of filtration involved may remove many of the factors that stimulate regeneration.

Regeneration models

Liver regeneration has been investigated mostly in rats, and *in vitro*. There have been found to be significant differences in the mechanisms involved *in vivo*, compared with those of *in vitro* cultured hepatocytes[9]. Cultured hepatocytes have very different physiological responses to those *in vivo*, and it has been increasingly recognized that the non-parenchymal cells, and their interaction with hepatocytes, may have a large and important role to play in *in vivo* regeneration[4]. For many regeneration factors the effects on liver *in vivo* are not known. Many of the substances involved are not specific to the liver and may be present without liver regeneration taking place, rendering *in vivo* studies confusing. Additionally, many cannot be analysed from serum.

Higgins and Anderson[10] published the earliest studies on regeneration in 1931, when they noted the remarkable capacity of the rat liver to regenerate after partial hepatectomy. This model of 70 per cent hepatic resection in rats has been used heavily in the investigation of hepatic regeneration. It is reproducible, and easily performed by removal of the left lateral and median lobes by ligating their vascular pedicles, leaving the remnant undamaged. Much work has subsequently been performed to investigate the factors that trigger the initiation of regeneration. In the case of surgical resection of rat liver, the process of regeneration begins within hours and is complete within 7–10 days.

The liver adapts almost instantly after partial hepatectomy to the resulting increased functional load per cell. Both positive and negative growth factors regulate hepatocyte proliferation, and the ratio between these factors may be more important than their absolute levels[5].

Stages of regeneration

Hepatocytes rarely divide under normal conditions in adult humans or animals. In adult liver only one in 1000 cells is in mitosis at any given time[11]. There are three main phases of liver regeneration. Cells are normally in a resting G0 state. After partial hepatectomy, all hepatic cells simultaneously undergo transition into G1 phase almost immediately. Hepatocytes enter S phase (DNA synthesis) roughly 12–15 h after partial hepatectomy. The G2 phase and mitosis (M phase) follow 6–8 h after DNA synthesis. Non-hepatocyte replication is usually delayed by approximately 24 h as a result of prolongation of their G1 phase[4]. During this initial phase of regeneration most hepatocytes will replicate at least once. When the original mass–volume ratio of the liver has been achieved, the hepatocytes revert to their quiescent G0 phase. The rat liver can almost double its size within 48 h of partial hepatectomy. Once the original liver mass is restored, liver regeneration stops abruptly[4].

The majority of hepatocytes are involved in this process, with each dividing at least once. However, this number decreases with increasing age, making regeneration slower and less complete in older animals[2]. Hepatocytes are heterogenous with respect to their gene expression and metabolic function[12]. This heterogeneity is maintained after liver regeneration and may, in part, be attributable to differences in blood flow and nutrient availability within normal hepatic architecture[2]. *In vivo*, the periportal hepatocytes are the first to begin replication, initially without any corresponding sinusoids or matrix. Cell clusters develop and replication spreads to the pericentral regions. Hepatocyte replication decreases by day 4 after partial hepatectomy, and thereafter non-parenchymal cells begin to recreate normal lobular hepatic architecture by dividing the cell clusters into cell plates surrounded by vascular spaces, sinusoids and spaces of Disse. The restoration of this complex microarchitecture may well exert some influence on the eventual arrest of the regenerative process[2]. During cell replication, hepatocytes do not appear to dedifferentiate, and are capable of continuing their metabolic and synthetic functions[5]. Regenerating liver has little reserve capacity, however, and does not efficiently remove excess amino acids or ammonia from the blood[13]. There is, therefore, a minimum volume of residual hepatocytes necessary if homoeostasis is to be maintained during replication.

Liver volume

The remaining functional liver volume limits liver regeneration, as the liver must be capable of maintaining its normal metabolic functions at the same time as undergoing cell division. The minimal volume liver remnant compatible with functional viability after liver resection has been the subject of much debate and several studies. Patients with greater than 80 per cent liver cell mass damage from drugs or viruses undergo complete liver regeneration if they survive the insult[6]. In the rat model operations involving a greater than 80 per cent reduction in liver mass are associated with a reduced rate of liver regeneration compared with the 70 per cent resection. The magnitude of DNA synthesis appears to vary as a function of tissue deficit to a certain degree[14,15].

In fulminant hepatic failure a hepatocyte volume fraction of less than 12 per cent is associated with a high mortality rate. Studies in rats have predicted a minimal hepatic energy charge; below this level regeneration does not proceed as the metabolic demands of the liver take precedence[16]. Similar methods for predicting the energy balance of liver remnants have been calculated for humans[17]. However, survivable 90 per cent liver resections have been performed successfully in rats[18], and have also been reported in humans[19].

Regeneration in disease

Restoration of normal liver architecture usually occurs after removal of the injurious factors causing liver damage. However, in the presence of continued injury, replication of hepatocytes, fibrosis, vascular abnormalities, and cirrhosis and/or cancer may ensue[20]. There is evidence to suggest that the mechanisms of regeneration may vary depending on the type of insult that the liver sustains. In the partial hepatectomy model, the remaining liver substance is undamaged, in contrast, for instance, to the damage sustained from carbon tetrachloride or viral hepatitis, which is spread throughout the parenchyma[4]. If the reticular framework of the liver is destroyed during liver injury then the regenerative process may lead to fibrosis and loss of normal liver architecture as well as cell replication; such is the case in cirrhosis. This again adds weight to the idea that the interaction between hepatocytes and non-parenchymal cells may be important for adequately controlled regeneration. Liver disease due to extrahepatic biliary obstruction causes localized periportal fibrosis, with destruction of small intrahepatic ducts, proliferation of bile ducts, portal fibrosis and eventually results in lobular distortion.

The massive necrosis associated with fulminant hepatic failure from viral hepatitis usually leads to death if liver transplantation is not performed. With chronic or mild necrosis and inflammation associated with hepatitis B or C, however, hepatocyte replication and fibrosis results. The fact that hepatocellular carcinoma in humans is usually associated with chronic liver disease, such as cirrhosis and viral hepatitis, suggests that repeated hepatocyte replication may cause disorder of the genes that regulate the cell cycle, leading to malignancy[21]. Telomerase activity, which is associated with cell replication, is negligible in normal liver but is slightly increased in hepatitis and cirrhosis, and markedly increased in hepatocellular carcinoma[22]. Neoplasia may be produced in this situation by alteration of DNA as well as inappropriate or increased expression of oncogenes[20].

Patients with cirrhosis have insufficient hepatocyte function to meet the increased metabolic demands after partial hepatectomy[17], and have significantly reduced levels of hepatic regeneration after liver resection, making them extremely vulnerable to posthepatectomy liver failure. Regeneration is often defective and may not occur at all in severe disease; conversely there may simply be a delay in full regeneration. Hyperbilirubinaemia tends to be prolonged, with extreme rises in serum bilirubin in patients who ultimately do not survive resection. Cirrhotics also become severely protein deficient after operation, a feature that is not usually seen in patients with normal liver function[7]. Rats with fatty livers also have reduced liver regeneration after partial hepatectomy and are much less tolerant of ischaemia[23]. DNA synthesis is impaired when there is coexistent pancreatic disease, but this can be increased by the administration of insulin and glucagon[24].

Initiation

The process of regeneration is considered to be divided into several stages, all of which are dependent on the presence or absence of a number of factors, acting in a cascade-like fashion. After partial hepatectomy or toxic liver injury, the regenerative response is orchestrated by the release of cytokines and growth factors, with subsequent increases in activity of growth response genes and telomeres[20]. Telomeres are repeat sequences of DNA at the ends of chromosomes that protect chromosomes from digestion, thereby preventing DNA loss; they are involved in ceasing replication. The construction of telomeres is dependent on the enzyme telomerase, which is not normally expressed by mature hepatic cells, except during replication. Telomerase, however, is expressed by 80 per cent of malignant cells and is often used as a marker of early malignant change[25].

Most hepatocytes are in a state of quiescence and require priming before undergoing replication. A number of factors involved in replication are present in the circulation, even when replication is not stimulated, suggesting that hepatocytes do not react to these factors unless they have been primed. Priming, or initiation, is controlled by a series of genes, which act within minutes of partial hepatectomy or on exposure to complete mitogens (see below). This stage may be itself divided into early and late stages.

The early stage is stimulated by proto-oncogenes, such as c-*fos*, c-*myc* and c-*jun*; these are transcriptional regulators. Thus is the cell primed for proliferation, but this stage can easily be reversed and its progression to cell division is dependent on the presence of other signalling factors. If these factors are absent, the cell simply returns to its quiescent phase[4]. Delayed, or late, initiation occurs several hours later, and is controlled by the induction of genes requiring protein synthesis, such as *p53*[4]. Other factors, such as an increase in ornithine decarboxylase activity, which is involved in the stabilization of messenger RNA (mRNA), influence the late stages of initiation, beginning at 1 h after partial hepatectomy and reaching a peak at 4 h. These factors are often sensitive to translation inhibitors[26]. The exact signal that induces the activation of these processes remains to be determined. It is thought that loss of functional liver mass after partial hepatectomy stimulates the release of cytokines, which in turn initiate DNA synthesis and regeneration by induction of appropriate genes.

Cytokines

The liver is a recognized target organ for proinflammatory cytokines such as tumour necrosis factor (TNF) α, interleukin (IL) 1 and IL-6. These cytokines are released within minutes of partial hepatectomy from non-parenchymal liver cells[27], and induce hepatocytes to synthesize further acute-phase proteins, mainly protease inhibitors, via activation of hepatocyte DNA-binding proteins. TNF-α binds to receptors on non-parenchymal liver cells and induces the synthesis of other cytokines, including IL-6. IL-6 is a common, multifunctional cytokine, which is produced in local tissues as part of the acute-phase response after a variety of systemic insults, such as trauma or acute infection. It acts on various cells and is involved in the differentiation of B cells, T cells and osteoclasts as well as hepatocytes. It has also been found to have a role in the growth and development of some tumours, such as renal cell carcinoma and Kaposi's sarcoma[28].

In liver regeneration, IL-6 is thought to result in enhanced transcription, triggering hepatocytes to leave their quiescent state (G0) and enter a prereplicative phase (G1), as well as being involved at further stages of replication. Once the hepatocytes have been initiated, exposure to further mitogens allows DNA synthesis to occur[27]. Expression of IL-6 appears to be essential for the priming of hepatocytes[28]. Serum levels of both TNF-α and IL-6 are raised within the first few hours after partial hepatectomy, despite DNA synthesis being delayed until 24 h[23]. In mice with IL-6 knockout genes, there is impaired DNA synthesis and an abnormal G1 phase after partial hepatectomy, leading to liver failure. This suggests that IL-6 has a leading role in the induction of hepatocyte proliferation[29,30]. The administration of IL-6 to TNF-α knockout mice has been shown to induce regeneration; however, the reverse effect in IL-6 knockout mice is not seen. This suggests that the role of TNF-α is much earlier in the regenerative process than that of IL-6[23]. IL-6 has also been found to protect hepatocytes against transforming growth factor (TGF) β-induced apoptosis[31].

Progression

Once the cell has been primed, the progression to G1 phase is dependent on the presence of continued stimulation by mitogens, such as epidermal growth factor (EGF), TGF-α, and insulin and glucagon. The effects of growth factors are thought to be short range and their mode of action may be dependent on the metabolic state of the hepatocytes and the presence or absence of other effectors[32]. When progression occurs, the cell proceeds to DNA synthesis, as once it has entered the S phase it is committed to undergo replication. In animal studies, peak rates of mitosis have been recorded at 24–48 h in rats, and at 4 days in dogs, after 70 per cent hepatectomy[7]. However, very few data on this topic exist for humans for obvious reasons; repeated biopsy of post-operative patients is hardly ethical. It is thought that there may be different pathways of stimulation to progression in liver injury without hepatocyte loss (toxic or viral injury)[33].

Complete mitogens

Complete mitogens are defined as substances that are capable of stimulating hepatocytes in culture to undergo DNA synthesis. Examples include EGF, TGF and, the most potent of all, hepatocyte growth factor (HGF). Levels of all these factors are markedly increased after 70 per cent partial hepatectomy and the infusion of serum from partially hepatectomized rats can induce DNA synthesis in normal rats[32]. Only HGF and TGF-α are able to stimulate hepatocytes to replicate in culture. Each of these complete mitogens can stimulate DNA synthesis in cultured hepatocytes. This effect can be potentiated *in vitro* by several incomplete mitogens (or co-mitogens) such as insulin, glucagon, adrenaline and noradrenaline[32,34]. If hepatocytes are exposed to complete mitogens in the absence of liver injury, there is little increase in the expression of immediate early genes[33]. Liver hyperplasia, however, can be induced by these agents, and this regresses on mitogen withdrawal. This suggests that, without liver injury, replication can occur via a different pathway[33].

Hepatocyte growth factor

HGF appears to be the most potent mitogen of all. Levels are greatly increased in blood and liver in cases of extensive liver damage. It is synthesized and secreted by a number of tissues as well as by non-parenchymal liver cells, particularly Kupffer cells. It is not found in hepatocytes, suggesting that it acts in a paracrine fashion. Its action is augmented in the presence of insulin, glucagon and EGF[6,32].

It is, however, a non-specific growth factor and many body tissues contain mRNA for HGF; it is capable of stimulating many kinds of epithelial cell, including kidney tubule cells and melanocytes. Particularly high levels of HGF are found in patients with fulminant hepatic failure, with the highest levels occurring in those who do not survive. This may represent maximal stimulation in patients who have sustained a lethal level of hepatic injury, which is ultimately fatal. An alternative explanation is that it simply represents the release of HGF from damaged liver cells, giving spuriously high circulating levels. High levels are also found in patients with chronic renal failure undergoing long-term haemodialysis, who show no evidence of liver injury or regeneration[35]. Interestingly, despite these very high levels, and the presence of HGF receptors in organs other than the liver, this does not produce a growth response in any other tissues. The reason for this is still obscure[4].

Transgenic mice that overexpress HGF have correspondingly high levels of c-*myc* and c-*jun* mRNA, suggesting that they may have some role in the induction of HGF action. These mice recover in half the normal time after partial hepatectomy. This tissue response can be suppressed by increasing doses of anti-HGF antibody *in vitro*[4]. Transgenic HGF knockout mice have been found to die *in utero* with atrophic livers[36].

Transforming growth factor *α*

TGF-α is also produced by non-parenchymal liver cells, mainly Kupffer cells. It is capable of increasing DNA synthesis *in vitro*[20]. It is similar to EGF in both its structure and its receptor. An increase in TGF mRNA occurs 4 h after partial hepatectomy, and peaks at 18–24 h[3,37]. Transgenic mice that overexpress TGF-α have significantly enlarged livers in infancy. However, this effect is lost in older mice, suggesting this may be simply a postnatal effect[4]. Of those transgenic mice that express TGF-α, 50–70 per cent develop hepatocellular tumours by 18 months. In contrast, transgenic mice expressing HGF have no increased incidence of tumours; HGF has actually been found to suppress the growth of many hepatocellular carcinomas *in vitro*[38,39].

Epidermal growth factor

EGF induces cultured hepatocytes to synthesize DNA. This effect is augmented by insulin. Administration of EGF and insulin increases DNA synthesis after partial hepatectomy in cirrhotic rats[40].

Hepatic stimulatory substance

Hepatic stimulatory substance is able to stimulate DNA synthesis only in those cells that have previously been primed. However, it is a potent mitogen for malignant hepatocytes[41]. It appears to be liver specific, in that it has no effect on other organs either *in vivo* or *in vitro*, and is secreted by the liver itself[42,43]. *In vitro* studies have detected a synergistic effect with EGF[4].

Co-mitogens

Co-mitogens have no direct stimulatory effect on hepatocyte proliferation on their own, but are capable of enhancing the effect of complete mitogens and reducing the effect of inhibitory substances. The latter include hormones and neurotransmitters, such as insulin, glucagon, noradrenaline, adrenaline, and thyroid and parathyroid hormones, as well as calcium and vitamin D[2]. Insulin-like growth factors, or somatomedins, are produced in the liver in response to growth hormone and are thought to be involved in the progression of regeneration rather than its initiation[32].

In 1975 Bucher and Swaffield[44] found that eviscerated rats had much lower rates of DNA synthesis after partial hepatectomy than normal rats, and that this effect could be reversed by the administration of insulin and glucagon. This was confirmed by subsequent studies, in which somatostatin (an inhibitor of insulin and glucagon secretion) was administered preoperatively, resulting in the inhibition of DNA synthesis; DNA synthesis was restored by the subsequent administration of both hormones[45].

Noradrenaline can enhance the effect of other growth factors on regenerating hepatocytes, as can several other hormones. Thyroid hormone does not specifically affect proliferation, but it does affect the overall metabolic state[32]. Parathyroid hormone has been found to have an effect on cells in the later stages of regeneration[46].

Nutrient availability is also thought to alter DNA synthesis. In rats, hepatocyte proliferation exhibits a circadian variation, which is dependent on feeding behaviour. Hepatocyte replication has been inhibited by food deprivation and reactivated by refeeding. This effect may be triggered by certain specific amino acids[47,48]. Levels of certain amino acids increase markedly in the first 4 h after liver resection and it has been suggested that this may be important for the increased synthesis of pyrimidines in the regenerating liver[5]. It has been demonstrated that amino acid overload *per se* induces DNA synthesis in the liver of rats maintained on protein-deficient diets[49].

Inhibitory factors

TGF-β is a multifunctional cytokine that can have either inhibitory or stimulatory effects, depending on cell type and conditions. It cancels the effects of TGF-α when administered at the same time, but has no effect on any of the other complete or incomplete mitogens, such as HGF or insulin[50]. TGF-β is also able to stimulate fibrogenesis in the liver[4]. It is produced by both hepatocytes and non-parenchymal cells, but requires cleavage from its binding protein by plasmin for activation[11]. Normal hepatocytes cannot activate TGF-β, but those undergoing regeneration can.

Administration of TGF-β to rats after partial hepatectomy inhibits replication for up to 22 h, after which time the hepatocytes begin to replicate again[51]. Transgenic mice that overexpress TGF-β have delayed regeneration and eventually develop hepatocellular cancer[52]. TGF-β levels are increased at 4 h after partial hepatectomy, with a peak at 72 h, suggesting that its action may be in the later stages of the regenerative process, perhaps by inducing apoptosis[4].

Liver growth is also inhibited by chalones, such as hepatocyte proliferation inhibitor and IL-1β, both of which decrease hepatocyte proliferation *in vitro*[4,26].

Discussion

Although great advances have been made over the past few years in understanding the remarkable ability of the liver to regenerate, significant gaps in knowledge still exist. The liver itself is such a complex organ, with well over 5000 different functions, that it would be unreasonable to imagine that the regenerative process would be under the control of any single liver-specific factor. This complexity, combined with the fact that many of the regenerative factors involved are not readily detected in the blood, or rather that they are present even when regeneration is not taking place, has precluded adequate human *in vivo* study of the processes involved. With the further development of gene sequencing and the advent of more specific tests for the relevant factors, the situation should improve. Many other substances that have not been discussed in this review are also thought to have roles in enhancing the liver's response to regeneration. However, the sheer number of substances that may, or may not, have a role in regeneration makes it difficult to focus on any single factor, and to attribute to it an affect without interaction from other substances.

These problems, combined with the obvious difficulty of human investigation, have resulted in almost all regeneration data being produced from either the rat partial hepatectomy model or from *in vitro* hepatocyte cultures. This is not without its drawbacks, as rat physiology is significantly different from that of humans; for instance, the rat liver undergoes significantly faster regeneration. There are also significant data to suggest that the *in vitro* models bear little resemblance to *in vivo* processes, mainly owing to the lack of normal hepatocyte to non-parenchymal cell architecture and interaction. Very few data are available from large animal models, but information from such a model would probably better reflect the human situation. Certainly further *in vivo* studies are required. Advances in understanding of molecular biology and in gene regulation and sequencing will, no doubt, eventually establish how regeneration factors are able to stimulate liver cells so rapidly after injury, and how the correct mass-to-liver ratio is determined at the conclusion of regeneration.

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Systematic review of the efficacy and safety of colorectal stents

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Background: Colorectal stents are being used for palliation and as a 'bridge to surgery' in obstructing colorectal cancers.

Methods: A systematic review of the published data on stenting for the treatment of colorectal obstruction was carried out by searching Medline and other online databases for the period from January 1990 to December 2000. A total of 58 publications (case series, single case reports and reviews) was found, of which 29 case series were included in the analysis. Technical and clinical success, complications and reobstruction, both in palliation and as a 'bridge to surgery', were assessed. Both descriptive statistics and pooled analyses were carried out.

Results: Pooled results showed that stent insertion was attempted in 598 instances. Technical success was achieved in 551 (92 per cent) and clinical success in 525 (88 per cent). Palliation was achieved in 302 (90 per cent) of 336 cases, while 223 (85 per cent) of 262 insertions succeeded as a 'bridge to surgery' (95 per cent had a one-stage surgical procedure). There were three deaths (1 per cent). Perforation occurred 22 times (4 per cent). Stent migration was reported in 54 (10 per cent) of 551 technically successful cases. The rate of stent reobstruction was 52 (10 per cent) of 525, mainly in the palliative group.

Conclusion: Evidence suggests that colorectal stents offer good palliation, and are safe and effective as a 'bridge to surgery'. Stent usage can avoid the need for a stoma, and is associated with low rates of mortality and morbidity. Dilatation of malignant strictures at the time of stent placement appears to be dangerous and should be avoided.

Paper accepted 9 April 2002

British Journal of Surgery 2002, **89**, 1096–1102

Introduction

Self-expanding metal stents have been used in oesophageal, biliary, hepatic and vascular obstructions. Technological advances and the introduction of flexible stents with a larger lumen have facilitated their use in colonic obstruction; colonic stents were first used by Dohmoto[1] in 1991.

Up to 85 per cent of acute colonic obstructions are due to malignancy, and between 10 and 30 per cent of patients with colonic cancer present with obstructive symptoms[2]. Emergency operation is associated with high morbidity and mortality rates[3], and often results in a temporary or permanent colostomy, which has an impact on quality of life[4]. Only 40 per cent of left-sided malignant colonic obstructions can be treated with surgical resection without any need for a stoma[5]. Stent deployment can avoid the need for a stoma by achieving adequate decompression to allow surgery in elective conditions.

Tejero *et al.*[6] described the use of stents as a 'bridge to surgery' in 1994. Other non-surgical modalities, such as balloon dilatation, laser ablation and decompression tubes, have been shown to be of limited effectiveness[7].

Colorectal stents, however, seem to offer a reasonable alternative or adjunct to surgical intervention. Furthermore, stenting is a logical method for palliation if metastatic disease is discovered[5] as a result of full staging after decompression of the obstruction. The present work is a systematic review of self-expanding metal stents in colorectal obstruction; it examines the clinical evidence for their efficacy and safety.

Methods

A literature search on Medline, Embase and the Cochrane Library was performed for the period from 1 January 1990 to 31 December 2000. It started in January 2001 and combined the following search terms: colon, obstruction or stenosis, stents, endoprosthesis or prosthesis. In addition, abstracts from two major gastroenterological congresses were handsearched and the references of the retrieved articles were reviewed. Particular authors were contacted when necessary.

The literature search retrieved a total of 58 publications: 38 case series, 11 single case reports, and nine letters, editorials or reviews. Of the 38 case series, 29 were included (*Table 1*) and nine excluded (*Table 2*). The 11 single case reports were not taken into account. Only two studies were found to contain information on economic variables[38,45].

Articles in languages other than English were included, as were all case series that reported information on the following outcomes: technical success (successful stent placement and deployment) and clinical success (colonic decompression within 96 h without endoscopic or surgical reintervention), complications (death, perforation, migration, bleeding and pain) and reobstruction. In addition, data on study population (demographics, type and location of lesion) and the type of stent used were extracted.

Publications containing primary data were excluded for the following reasons: no detailed information on the specified endpoints, publications on patients whose data were also included in subsequent articles, and single case reports. The retrieved literature was also reviewed with regard to information on the cost and cost-effectiveness of colorectal stenting.

A database in Excel® (Microsoft, Redmond, Washington, USA) was set up. Descriptive statistics (quartiles, medians, ranges) were applied and weighted averages (weighted by study population) were calculated for the population pooled from the 29 studies included (pooled analysis).

Results

The following results are based on the 29 case series included in the review. For each outcome, both weighted averages from the pooled population and the interquartile range are presented. Individual study results are presented in *Table 1*. Stent placement was attempted in 598 patients, of whom 48 per cent were women. The mean age was 70 (range 23–98) years. There were 336 (56 per cent) palliative procedures and 262 (44 per cent) treatments as a 'bridge' to elective operation. Information on aetiology was available for 567 patients: 552 (97 per cent) had malignant lesions and 15 (3 per cent) had benign lesions, of which 11 were due to diverticular disease and four to benign stricture. The majority of stent placements were for left-sided lesions (*Table 3*).

Technical and clinical success

Technical success was defined as successful stent placement and deployment. Clinical success meant colonic decompression within 96 h without endoscopic or surgical reintervention after successful stent placement and deployment. This time interval was chosen because it was integral to the definition used in nearly all the papers reviewed.

Technical success was achieved in 551 (92 (interquartile range (i.q.r.) 88–100) per cent) of 598 patients and clinical success was reported in 525 (88 (i.q.r. 83–93) per cent) of 598 patients (*Table 4*). Clinical success was achieved in the palliation group in 302 (90 per cent) of 336 instances, and in the 'bridge to surgery' group in 223 (85 per cent) of 262 instances. A total of 212 (95 per cent) of 223 clinically successful 'bridge to surgery' cases were associated with a one-stage colonic resection; mean time to operation in this group was 8·9 (range 2–115) days

Technical and clinical failure

Technical failure was reported in 47 (8 per cent) of 598 patients. The main causes were inability to place a guidewire across the lesion in 36 cases, malposition in four and perforation in two; there was inadequate information for the remaining five patients. After technically successful stent placement, clinical failure occurred in 26 (5 per cent) of 551 patients. The main causes were perforation in eight, persistent obstructive symptoms in ten, and adhesions of the colonic wall to the stent in three; data on the remaining five were inadequate.

Mortality

Three (1 per cent) of the 598 patients died (*Table 4*). Two patients needed a laparotomy; one had a perforation and the other did not decompress. Both died in the early postoperative period. One patient was stented successfully but died 12 days later from a perforation.

Perforation

As shown in *Table 4*, perforation occurred in 22 (4 (i.q.r. 0–7) per cent) of 598 patients. A total of 21 studies (493 patients) did not practise balloon predilatation, while eight studies (105 patients) did this electively; these eight studies reported a higher incidence of perforation. The incidence of perforation in the non-balloon dilatation group was 12 (2 per cent) of 493, and in the dilatation group it was 10 (10 per cent) of 105 ($P < 0{\cdot}05$, χ^2 test).

Table 1 Case series and individual study results

Reference	Year	Stent used*	Total population	Palliative	'Bridge to surgery'	Technical success†	Clinical success‡	Mortality	Perforation	Migration	Severe pain§	Severe bleeding¶	Reobstruction
Camunez *et al.*[8]	2000	Oesophageal Wallstent™	80	42	38	70	67	1	4	3	1	0	2
Mainar *et al.*[9]	1999	Oesophageal Wallstent™	71	0	71	66	63	0	1	0	0	0	0
Fernandez Lobato *et al.*[10]	1999	Oesophageal Wallstent™	41	41	0	41	38	0	0	2	0	0	5
Tejero *et al.*[11]	1997	Oesophageal Wallstent™	38	13	25	38	35	0	0	0	0	0	3
Zollikofer *et al.*[7]	2000	Vascular and Enteral Wallstent™	30	9	21	26	24	0	1	3	—	—	7
Cole *et al.*[12]	2000	Enteral Wallstent™	28	20	8	25	24	0	2	3	0	0	0
Baron *et al.*[13]	1998	Various – Wallstent™, Ultraflex™, Esophacoil ™	25	15	10	23	21	0	4	5	0	0	2
De Gregorio *et al.*[14]	1998	Oesophageal Wallstent™	24	24	0	24	23	0	0	0	0	0	3
Law *et al.*[15]	2000	Uncovered oesophageal Wallstent™	24	18	6	24	23	0	1	3	0	0	4
Choo *et al.*[16]	1998	Totally and partly covered Choo stent™	20	8	12	18	18	0	0	4	0	0	0
Diaz *et al.*[17]	1999	Oesophageal Wallstent™	16	16	0	16	15	0	0	3	0	2	3
Rocca *et al.*[18]	2000	Enteral Wallstent™	16	4	12	14	13	0	0	—	0	0	—
Repici *et al.*[19]	2000	Covered Ultraflex™	16	16	0	15	15	0	1	2	—	—	1
Saida *et al.*[20]	1996	Z Stent™	15	0	15	12	12	0	2	1	0	0	0
Canon *et al.*[21]	1997	Esophacoil™, Ultraflex™, biliary and tracheal Wallstent™	13	9	4	13	12	0	2	3	0	0	2
Spinelli *et al.*[22]	1993	Z Stent™	13	13	0	12	12	0	1	0	0	0	2
Liberman *et al.*[23]	2000	Enteral Wallstent™	12	12	0	8	8	0	0	2	0	0	1
Adamsen *et al.*[24]	2000	Choo stent™	12	12	0	11	11	0	0	3	0	0	11
Rey *et al.*[25]	1995	Ultraflex™	12	3	9	10	10	1	0	2	0	0	1
Knoepfle *et al.*[26]	1998	Oesophageal Wallstent™	11	0	11	8	7	0	0	2	0	0	1
Buchanan *et al.*[27]	2000	Enteral and oesophageal Wallstent™, Memotherm™	11	7	4	10	10	0	0	1	0	0	0
Tamim *et al.*[28]	2000	Enteral Wallstent™	11	11	0	9	9	0	0	3	0	0	0
Tack *et al.*[29]	1998	Boston prototype	10	10	0	9	9	0	1	3	1	0	2
Wholey *et al.*[30]	1998	Tracheobronchial Wallstent™	10	4	6	10	9	1	0	4	0	0	0
Fava *et al.*[31]	1999	Wallstent™	9	7	2	9	9	0	0	0	0	0	0
Desroches *et al.*[32]	1999	Wallstent/Ultraflex™	8	2	6	8	8	0	1	0	0	0	0
Miyayama *et al.*[33]	2000	Ultraflex™	8	8	0	8	7	0	0	1	1	1	2
Wallis *et al.*[34]	1998	Oesophageal Wallstent™	7	5	2	7	7	0	1	1	0	0	0
Arnell *et al.*[35]	1998	Enteral Wallstent™	7	7	0	7	6	0	0	0	0	0	0

*Wallstent™ and Ultraflex™ (Boston Scientific Corporation, Galway, Ireland); Esophacoil™ (Medtronic, Eden Prairie, Minnesota, USA); Choo stent™ (MI Tech, Seoul, Korea); Z Stent™ (Wilson-Cook Medical, Winston-Salem, North Carolina, USA); Memotherm™ (CR Bard, Billerica, Massachusetts, USA). †Stent successfully placed and deployed. ‡Colonic decompression within 96 h without endoscopic or surgical reintervention. §Needing inpatient treatment or operation. ¶Requiring blood transfusion

Table 2 Excluded case series

Reference	Year	Study population	No. of stented patients*	Reason for exclusion
Castaneda-Zuniga[36]	1996	24	24	No detailed data in abstract
De Gregorio *et al.*[37]	1996	24	24	Data in De Gregorio *et al.*[14]
Binkert *et al.*[38]	1998	13	13	Data in Zollikofer *et al.*[7]
Mainar *et al.*[39]	1996	12	12	Data in Mainar *et al.*[9]
Rupp *et al.*[40]	1995	10	10	No detailed data given
Osaka *et al.*[41]	2000	7	7	No detailed data given
Soonawalla *et al.*[42]	1998	7	7	Data in Cole *et al.*[12]
Turegano-Fuentes *et al.*[43]	1998	11	7	Data in Camunez *et al.*[8]
Boorman *et al.*[44]	1999	6	6	Data in Cole *et al.*[12]
Total		114	110	

*Stent successfully placed and deployed

Table 3 Patient population and site of obstruction

	No. of patients ($n = 598$)
No. having palliation	336
No. having 'bridge to surgery'	262
Site of obstruction*	
Rectum	113 (21)
Rectosigmoid	335 (61)
Descending colon up to splenic flexure	77 (14)
Transverse colon	9 (2)
Ascending colon including hepatic flexure	4 (1)
Previous colorectal anastomosis	7 (1)

Values in parentheses are percentages. *Information available for 545 (91 per cent) of 598 patients

Stent migration

Stent migration occurred after 54 (10 (i.q.r. 3–22) per cent) of 551 technically successful insertions (*Table 4*). Migration occurred within 3 days in 14 (26 per cent) of 54 patients; the remaining 40 occurred after 3 days. Management consisted of stent removal and no further intervention in ten (19 per cent) of 54 patients, stent reinsertion in 11 (20 per cent), and operation in six (11 per cent). Twenty-six (48 per cent) of all migrated cases needed no further intervention, either because the patients proceeded as planned to operation despite stent migration or displacement, or because the tumour had shrunk as a result of chemotherapy. Some patients remained under observation but, despite migration, no reobstruction occurred before death or the conclusion of follow-up. Key factors increasing the likelihood of migration were laser pretreatment, chemotherapy and benign tumour. The pooled analysis showed that 40 per cent of patients with migrated stents had had laser pretreatment or chemotherapy, or, in a few cases, stenting for a benign lesion.

Reobstruction

Overall, reobstruction occurred in 52 (10 (i.q.r. 0–15) per cent) of 525 cases (*Table 4*). Reobstruction generally affected palliative patients (16 (i.q.r. 0–23) per cent); only three patients in the 'bridge to surgery' group had reobstruction. The causes of reobstruction in 52 patients included tumour growth in 32 (62 per cent), stent migration in seven (13 per cent) and faecal impaction in 13 (25 per cent).

Bleeding

Bleeding occurred in 27 patients (5 (i.q.r. 0–5) per cent), 24 of whom required no treatment and had a spontaneous resolution. Three patients required blood transfusion (*Table 4*).

Pain

Abdominal or rectal pain was reported by 31 (5 (i.q.r. 0–8) per cent) of 598 patients. Only three required inpatient analgesia; 28 resolved either spontaneously or with oral analgesia (*Table 4*).

Cost-effectiveness

Only two publications examined the cost impact of stenting compared with surgical decompression[38,45], and both described cost savings for the stented group. A UK study[45] estimated that the cost of a palliative case was less than half of that of a surgically decompressed case (£1445 *versus* £3205). The cost of the 'bridge to surgery' situation was reduced by 12 per cent compared with a two-stage operative procedure (£5035 *versus* £5720). A Swiss study[38] reported savings of up to 20 per cent for preoperative stent placement compared with surgical management.

Table 4 Systematic review: interquartile ranges and pooled analyses

	Interquartile range across 29 case series (%)			Pooled analysis of 598 patients	
	25th percentile	Median	75th percentile	No. of patients	Weighted mean (%)
Technical success (successful stent placement and deployment)	88	92	100	551 of 598	92
Technical failure				47 of 598	8
Primary clinical success (colonic decompression with endoscopic or surgical reintervention)	83	90	93	525 of 598	88
Clinical failure				26 of 598	4
All severe complications (death, perforation, severe bleeding requiring transfusion, severe pain)	0	3	13	31 of 598	5
Death	0	0	0	3 of 598	1
Perforation	0	0	7	22 of 598	4
Bleeding					
All, including severe	0	0	5	27 of 598	5
Severe	0	0	0	3 of 598	1
Not severe	0	0	5	24 of 598	4
Pain					
All	0	0	8	31 of 598	5
Severe	0	0	0	3 of 598	1
Not severe	0	0	3	28 of 598	5
Migration	3	13	22	54 of 551	10
Reobstruction					
All patients	0	9	15	52 of 525	10
Palliated patients	0	13	23	49 of 302	16
'Bridge to surgery' patients	0	0	0	3 of 223	1

These cost savings were due mainly to the shorter hospital stay associated with stenting. Other factors were fewer surgical procedures, reduced operating room time and fewer days in intensive care. The hidden cost of stoma care in the community cannot be overlooked; about £200 per month is required for disposable stoma bags for each patient[45].

Discussion

Malignancy is the major cause of acute colonic obstruction[2,46] and up to 50 per cent of patients are between 70 and 89 years old[46]. Surgery on the unprepared bowel carries high morbidity (10–36 per cent) and high mortality (6–30 per cent) rates; elective procedures have lower morbidity (4–14 per cent) and mortality (1–7 per cent) rates[3]. The UK National Audit[46] showed that 59 per cent of patients with a left-sided obstruction had a successful one-stage surgical resection, and 41 per cent had a Hartmann procedure. It may be that stents will have a role complementing surgery for malignant colonic obstruction if they can be shown to reduce immediate mortality and morbidity successfully without compromising long-term survival.

This systematic review has shown that stents were placed successfully in 92 per cent of patients in whom insertion was attempted; clinical success was achieved in 88 per cent.

Palliation was achieved in 90 per cent of patients and stent placement was successful as a 'bridge to surgery' in 85 per cent. Ninety-five per cent of the 'bridge to surgery' group went on to have a single-stage colonic resection, thereby avoiding a colostomy. Harris *et al.*[47] stated that while stents can aid palliation their role as a 'bridge to surgery' remains to be defined. This review clearly shows that stents are safe and effective in decompressing colonic obstruction, allowing the patient to proceed to a one-stage surgical resection.

Colostomy has an associated morbidity rate of up to 34 per cent[48], and only 60 per cent of patients go on to have a stoma reversal operation[2]. The problems associated with managing a stoma, a quality-of-life issue[48], can be avoided by successful stent placement; this is particularly important in patients who have co-morbidity and who are often elderly with arthritic changes that make stoma management difficult.

This review shows that stenting has low associated mortality and morbidity rates. The UK National Audit[46] recorded that patients undergoing surgical resection for left-sided colonic obstruction had an operative mortality rate of 12·9 per cent. Stenting has a low mortality rate of 1 per cent, and evidence shows that it is a safe method of achieving decompression to optimize a patient for operation.

Perforation occurred in 4 per cent of stented patients, with a higher incidence in those having balloon predilatation. Balloon dilatation cannot therefore be recommended. Fortunately, it is possible to achieve stent placement even in patients with tight strictures without employing dilatation when modern stents are used. In addition, as perforation is more likely to occur during guidewire manipulation, the introduction of a wide range of soft-tipped guidewires may contribute further to prevention of perforation.

It is of interest that most patients with stent migration remained asymptomatic and needed no further intervention. Migration was notably higher after laser pretreatment, after chemotherapy, and in patients with strictures of benign aetiology. All of these factors promoted loosening of the stent, but the outcome was benign as luminal compromise no longer existed. Furthermore, some of the stents used were not designed specifically for colorectal anatomy, and this might also have favoured migration. In the future, specifically designed colorectal stents should contribute to reducing migration.

Reobstruction was occasionally a problem in the palliation group. The main cause was the continuing neoplastic process blocking the stent lumen or growing around the stent.

In conclusion, evidence suggests that stents are effective and associated with low morbidity and mortality rates. They are a useful adjunct to colorectal surgery. However, dilatation of malignant strictures before their placement seems dangerous and should be avoided. A randomized controlled trial, and studies evaluating cost-effectiveness and quality of life, are needed for further assessment of stent efficacy.

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Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis

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Background: Microbial infection of the pancreatic tissue in patients with severe acute pancreatitis increases the morbidity and mortality rates. Colonization of the lower gastrointestinal tract and oropharynx with Gram-negative, but sometimes also Gram-positive, bacteria precedes contamination of the pancreas. The aim of this study was to determine whether lactic acid bacteria such as *Lactobacillus plantarum* 299 could prevent colonization of the gut by potential pathogens and thus reduce the endotoxaemia associated with acute pancreatitis.

Methods: Patients with acute pancreatitis were randomized into two double-blind groups. The treatment group received a freeze-dried preparation containing live *L. plantarum* 299 in a dose of 10^9 organisms, together with a substrate of oat fibre, for 1 week by nasojejunal tube. The control group received a similar preparation but the *Lactobacillus* was inactivated by heat.

Results: A total of 45 patients completed the study. Twenty-two patients received treatment with live and 23 with heat-killed *L. plantarum* 299. Infected pancreatic necrosis and abscesses occurred in one of 22 patients in the treatment group, compared with seven of 23 in the control group ($P = 0.023$). The mean length of stay was 13·7 days in the treatment group *versus* 21·4 days in the control group (P not significant).

Conclusion: Supplementary *L. plantarum* 299 was effective in reducing pancreatic sepsis and the number of surgical interventions.

Paper accepted 1 May 2002

British Journal of Surgery 2002, 89, 1103–1107

Introduction

Pancreatic necrosis, even if sterile, and pancreatic infection are independent determinants of organ failure and poor outcome in patients with severe acute pancreatitis[1]. Infected pancreatic necrosis occurs in 24 per cent of patients after 1 week and in 72 per cent after 3 weeks[2]. The mortality rate after pancreatitis is five to ten times higher if the necrotic tissue becomes infected[2,3]. Antibiotics[4–6], as well as various proinflammatory cytokine inhibitors[4], have failed to make a significant impact on the outcome. An effective treatment during the early course of acute pancreatitis that prevents the systemic inflammatory response syndrome is much needed[4].

Early enteral nutrition is known to reduce septic morbidity in conditions such as thermal injury[7], trauma[8] and major surgery[9]. Adherence to the old belief that pancreatic rest is important has significantly delayed the use of early enteral nutrition in severe pancreatitis. The experience with enteral nutrition in severe acute pancreatitis has recently been reviewed by Guillou[10] and Erstad[11]. A large controlled study of patients with pancreatitis showed that enteral nutrition significantly reduced septic complications, but made no difference to the rate of multiple organ failure or death[12].

Ingestion of specific fibre-fermenting lactic acid bacteria and fermentable fibre is known to reduce bacterial translocation, upregulate immune function, reduce the rate of infection, and limit the extent of cellular injury and tissue necrosis[13–15]. A significant reduction in sepsis rates and improved outcomes in upper abdominal surgery[16] and liver transplantation[17] have been reported with therapy. Treatment with a combination of *Lactobacillus plantarum* 299 and oat proved effective in preventing sepsis in experimental pancreatitis in rats[18]. The present study was undertaken to investigate whether early enteral nutrition and a daily enteral supply of *L. plantarum* 299 and oat fibre could improve outcome in patients with acute pancreatitis.

Patients and methods

Patients with acute pancreatitis admitted between January 1999 and March 2001 to the Surgical Department of Petz Aladár Teaching Hospital, Györ, Hungary were enrolled in the study. Inclusion criteria were a typical clinical picture including abdominal pain, laboratory signs of pancreatitis (plasma amylase level greater than 200 units/l; normal value less than 70 units/l) and a short duration of symptoms. Only patients admitted within 48 h after the onset of symptoms were included in the study. Patients with evidence of biliary tract disease and those who had urgent therapeutic intervention (endoscopic papillotomy, cholecystectomy and/or choledochotomy) were excluded. Patients with an acute exacerbation of chronic pancreatitis, those in whom the placement of a feeding tube was not possible, patients unable or unwilling to cooperate, and those who could not tolerate jejunal feeding were excluded. The severity of acute pancreatitis was assessed by means of the Glasgow score[19]; patients with a score of 3 or more were considered to have severe pancreatitis. A C-reactive protein (CRP) level greater than 150 mg/l was also regarded as a sign of severe pancreatitis.

The study was approved by the local ethics committee and written informed consent was obtained from all participants.

Enteral feeding

A nasojejunal feeding tube (duodenal set; Angiomed®, Karlsruhe, Germany) of calibre 14 F and length 150 cm was inserted on the day of admission and the final position checked by radiography. The tube was left for 7–10 days, but was unintentionally regurgitated in four patients and needed to be replaced. Three patients did not tolerate the feeding tube and removed it intentionally; they were excluded. Two patients developed a severe ileus and did not tolerate enteral feeding at all; they were also excluded from the study.

On admission, after consent was obtained, the patients were randomized into one of the following two treatment groups. Patients in the control group (enteral feeding and fibre) received enteral nutrition through the jejunal feeding tube with Nutrison Fibre® (Nutricia, Zoetermeer, Holland) by a gravity-driven continuous drip. The dose was gradually increased to a maximum within 2–3 days, when the goal of supplying 30 kcal/kg body-weight was reached. Enteral feeding was continued for a minimum of 7 days in all patients, before they returned to normal eating. A preparation consisting in 10^9 organisms of heat-killed *L. plantarum* 299 and 10 g oat fibre was supplemented twice daily via the feeding tube during the first 7 days.

Patients in the treatment group (enteral feeding with lactobacillus and fibre) were treated exactly as described for controls, except that live *L. plantarum* 299 in a dose of 10^9 organisms was supplied twice daily during the first 7 days.

Both the live and heat-killed preparations of *L. plantarum* 299 and oat fibre were produced by Nutricia, and provided for the study by AB Probi, Lund, Sweden.

Management of acute pancreatitis

Antibiotics were administered only when pancreatic infection was suspected or proven, or for severe complications such as organ failure. Infective complications were treated with imipenem with cilastatin, or in accordance with recommendations following culture and sensitivity analysis of isolated bacteria. Other adjuvant therapy was the same in the two patient groups, and followed generally accepted principles. No attempt was made to reduce gastric acidity, as low pH was considered important for control of microbial overgrowth in the stomach.

Outcome variables

Blood samples were taken on the day of admission, and on days 1, 2 and 7 thereafter. Routine laboratory determinations were made, together with CRP and blood gas analysis. Abdominal ultrasonography was performed on the day of admission and contrast-enhanced computed tomography (CT) on days 2 and 7. Pancreatic necrosis was defined as severe if it involved more than 30 per cent of the tissue of the gland. Bacterial infection of the pancreas was diagnosed by culture and Gram staining of samples obtained by CT or ultrasonographically guided fine-needle aspiration, or through direct samples from the pancreatic tissue if laparotomy was required. Microbiological studies were performed in all patients when infection was suspected as shown by fever, raised neutrophil count or early signs of organ failure.

The main outcome measures in the study were organ failure, septic complications requiring a surgical procedure, length of hospital stay and death.

Statistical analysis

The study was randomized and double-blind. It was designed to be discontinued when interim statistical analysis found a significant difference in favour of one of the groups. This happened when 45 patients had been enrolled; consequently the study was discontinued. Data were analysed with the Mann–Whitney *U* test, or the χ^2 test where appropriate. $P < 0·05$ was considered statistically significant.

Results

In total, 45 patients completed the study, 23 in the control group and 22 in the lactobacillus group. There were no significant differences between the two groups with regard to sex, age, aetiology of the pancreatitis, and time between onset of symptoms and hospital admission (*Table 1*). There were no significant differences between the two groups in terms of Glasgow score, CRP value, rate of pancreatic necrosis or rate of severe pancreatitis (*Table 2*).

Infections and other complications

There were no significant differences between the groups in the extent and frequency of pancreatic necrosis on CT. Necrosis was detected on the second day in eight patients, five in the control group and three in the lactobacillus group. On the seventh day a further 12 patients had signs of pancreatic necrosis, six in each group. Of 20 patients with pancreatic necrosis, less than 30 per cent of the pancreas was involved in eight patients, four in each group. Twelve patients had more than 30 per cent involvement, seven in the control group and five in the treatment group.

Bacteremia was documented in five patients, four in the control group and one in the lactobacillus group. Repeat aspiration showed positive cultures in seven controls and in one patient in the treatment group ($P = 0·023$). Chest infection was observed in four patients, two in each group. One patient in the lactobacillus group suffered urinary infection. On early sign of infection, antibiotics were indicated and administered in eight patients, seven in the control group and one in the lactobacillus group. A further five patients received antibiotics for severe organ dysfunction: two in the control group and three in the lactobacillus group (*Table 3*).

Four patients developed multiple organ failure, three of whom died: both patients in the control group and one of two in the lactobacillus group. Of the patients with multiple organ failure, two had infected and two had sterile necrosis.

The indications for surgical intervention were documented abscess or infected necrosis, but not sterile necrosis. Pancreatic surgery was required in seven patients with pancreatic infection in the control group, five with infected necrosis and two with an abscess. Necrosectomy was done in five patients and surgical drainage in two. Only one patient in the lactobacillus group needed intervention: percutaneous drainage followed later by surgical necrosectomy. This difference was statistically significant ($P = 0·046$).

Table 1 Clinical details of patients with acute pancreatitis

	Control group ($n = 23$)	Lactobacillus group ($n = 22$)
Mean(s.d.) age (years)	46·5(13·6)	44·1(11·1)
Sex ratio (M : F)	17 : 6	16 : 6
Aetiology		
Alcohol	16	13
Other	7	9
Mean(s.d.) duration of symptoms before admission (h)	21·4(14·1)	26·1(13·3)

Table 2 Severity of acute pancreatitis

	Control group ($n = 23$)	Lactobacillus group ($n = 22$)
Mean(s.d.) Glasgow score	2·8(1·5)	2·5(1·3)
Mean(s.d.) CRP level (mg/l)	188·7(108·3)	206·5(119·5)
No. with necrotizing pancreatitis	11	9
No. with severe pancreatitis	15	17

CRP, C-reactive protein

Table 3 Infective complications of acute pancreatitis

	Control group ($n = 23$)	Lactobacillus group ($n = 22$)
Systemic inflammatory response syndrome	6	11
Multiple organ failure	2	2
Positive aspiration culture	7	1*
Positive blood culture	4	1
Pancreatic abscess	3	0
Infected necrosis	4	1
Chest infection	2	2
Antibiotic therapy	9	4
Septic complication requiring operation	7	1*
Death	2	1

*$P < 0·05$ *versus* control (χ^2 test)

The mean duration of hospital stay was longer in the control group than in the treatment group (21·4 *versus* 13·7 days), but the difference was not statistically significant.

Discussion

There is evidence that enteral nutrition is beneficial in acute pancreatitis[20,21]. In a recent review, when compared to parenteral nutrition, enteral nutrition reduced the mortality rate (relative risk (RR) 0·56 (95 per cent confidence interval (c.i.) 0·05 to 5·62)), reduced hospital stay by 2 days (95 per cent c.i. 3·62 to 0·78) and reduced the risk of infection (RR 0·61 (95 per cent c.i. 0·29 to 1·28)). The present authors' recent study of 89 patients demonstrated that enteral nutrition significantly reduced the number of septic complications ($P = 0{\cdot}03$), but had no effect on the rate of multiple organ failure ($P = 0{\cdot}14$) or death ($P = 0{\cdot}13$) in patients with acute pancreatitis[12].

Enteral nutrition is currently regarded much less as a means of providing calories and nitrogen than as a way of modulating the acute-phase response and improving immune function. It has been concluded that about 75 per cent of immune function is localized in the gastrointestinal tract[13], which might explain why enteral nutrition is an excellent tool for immunomodulation. To be effective, enteral nutrition must be instituted at the earliest opportunity. It is known from studies of experimental pancreatitis that the therapeutic window is narrow and limited to the first hours after the onset of the disease[22]. Translocation both to the peritoneal cavity and to pancreatic tissue is observed in experimental pancreatitis in 60 per cent of the animals after 6 h and in 90 per cent after 24 h[23]. Intestinal motility is significantly reduced after 3 h and leakage of plasma protein to the peritoneum and significant translocation is observed after 6 h[24]. A significant reduction in anaerobic flora, including lactobacilli, is observed as early as 6 h after the onset of pancreatitis, and signs of enterobacterial overgrowth occur within 12 h[24,25]. Although such changes might occur later in humans, studies of early changes in various immune parameters, cytokines, coagulation factors and growth factors in acute pancreatitis support the concept that early nutritional intervention might be beneficial. Early enteral nutrition is not easy to achieve because many patients arrive in hospital more than 24 h after the onset of acute pancreatitis.

The rapid disappearance of commensal flora in acute pancreatitits combined with the overgrowth of potentially pathogenic micro-organisms is a reasonable rationale for early supplementation of lactic acid bacteria. Probiotics (lactic acid bacteria) are documented to have strong anti-infectious and immunomodulatory effects. Supplying only probiotics is not enough, as probiotic bacteria need substrate for their growth and function. Fibre acts as this substrate (prebiotics) and thus was administered concurrently.

In the present study only one of 22 lactobacillus-treated patients developed sepsis that required surgery, compared with seven of 23 in the control group of patients who received heat-killed lactobacilli. The single patient in the lactobacillus group who developed infection had signs on day 15 after admission, at a time when he had not received treatment for 8 days. Experience from these studies and others done in Berlin[16,17] indicates that treatment failure often occurs after lactobacillus ingestion has been discontinued. To be protective, treatment with probiotics and prebiotics should perhaps be continued for at least 2–3 weeks, or for as long as rectal cultures show colonization with potential pathogens.

The results of this study are in accordance with those of other studies. In a study of patients undergoing gastric and pancreatic surgery[16], the 1-month sepsis rate with live *L. plantarum* 299 was one of 15, compared with three of 17 patients receiving heat-inactivated *L. plantarum*. Eight of 16 patients who received parenteral nutrition with fibre and no lactobacillus developed sepsis ($P = 0{\cdot}001$). Similar results were obtained in patients undergoing liver transplantation[17]: four of 31 patients who received live *L. plantarum* 299 and fibre developed infection, compared with 11 of 34 given heat-killed *L. plantarum* 299 and fibre, and 15 of 32 treated with selective bowel decontamination ($P = 0{\cdot}017$).

Immunonutrition is in its infancy. This small study supports the assumption that the combined use of prebiotics and probiotics (synbiotics) could offer an effective tool to reduce morbidity in severe, emergency conditions such as acute pancreatitis, and in connection with extensive surgery. Present experience suggests that the treatment may be needed for longer than was the case in this study to have maximum effect.

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Randomized trial

Randomized clinical trial comparing quality of life after straight and pouch coloanal reconstruction

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Background: Functional results after rectal resection with straight coloanal anastomosis are poor. While most functional aspects are improved with coloanal J pouch anastomosis, it is still unclear whether this translates into better quality of life. The aim of this trial was to investigate health-related quality of life as a primary endpoint in patients undergoing sphincter-saving rectal resection.

Methods: Sixty-four patients were randomized to either straight (n = 32) or coloanal J pouch (n = 32) anastomosis. Patients were studied before operation, at the time of stoma reversal and at 3-month intervals for 1 year thereafter. Quality of life was measured using two generic (Gastrointestinal Quality of Life Index and European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30) and one disease-specific (EORTC QLQ-CR38) instruments. Functional results using a standardized score as well as manometric variables were recorded.

Results: Thirty-nine patients (19 with a pouch and 20 with a straight anastomosis) completed the trial. There was a marked difference between the two groups with regard to quality of life profile. Patients with a pouch reconstruction had a significantly better quality of life, particularly in the early postoperative period.

Conclusion: Patients undergoing low anterior rectal resection and coloanal J pouch reconstruction may expect not only better functional results but also an improved quality of life in the early months after surgery compared with patients who receive a straight coloanal anastomosis.

Paper accepted 9 May 2002

British Journal of Surgery 2002, **89**, 1108–1117

Introduction

Sphincter-saving procedures have become standard treatment in the surgical approach to most cancers of the middle and even lower third of the rectum[1–3]. However, functional results following low anterior resection with straight coloanal anastomosis are often poor. The incidence of early postoperative functional disorders is reported to be as high as 80–87 per cent[4,5]. To compensate for the loss of the rectal reservoir Lazorthes *et al.*[6] and Parc *et al.*[7] proposed coloanal J pouch reconstruction. Randomized trials that compared the J pouch with straight end-to-end coloanal anastomosis have shown functional superiority of the pouch, especially in the early months after surgery[8–11].

However, better functional results are not necessarily associated with better quality of life, as has been reported repeatedly in patients with various anorectal conditions[12–15]. As health-related quality of life is increasingly being recognized as an important endpoint in clinical trials[16–18], it was hypothesized that significant differences in bowel function should also be reflected in quality of life measurements. Therefore, the aim of this study was to assess quality of life longitudinally as a primary endpoint in patients undergoing rectal resection with different reconstruction techniques. Taken that potential differences might be very subtle and consequently difficult to detect, it was important to ensure that measurements were carried out at regular intervals, with special emphasis on the early postoperative phase during which functional differences are known to be more conspicuous[8–11].

Patients and methods

Study design

The study was designed as a single-centre randomized trial comparing two reconstruction methods following low anterior resection of the rectum. Randomization was

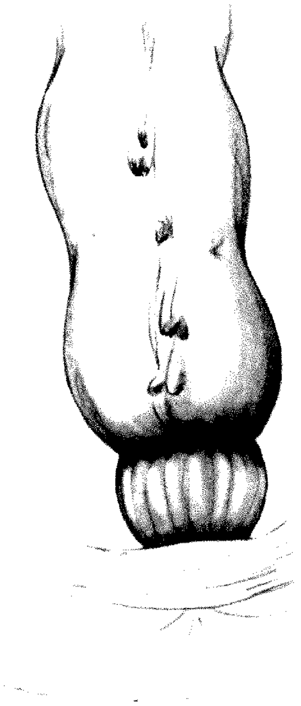

Fig. 1 Straight coloanal anastomosis. The descending colon is anastomosed end to end to the rectal remnant or proximal anal canal

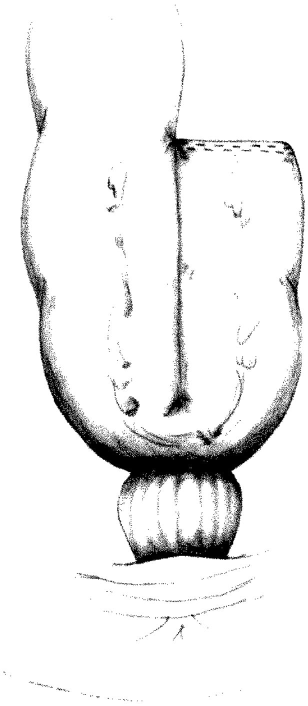

Fig. 2 Coloanal J pouch anastomosis. Before performing the anastomosis the descending colon is plicated in a J like fashion to create a neorectal reservoir

carried out using computer-generated random clusters, each comprising 20 consecutive patients. Patients were assigned intraoperatively to either straight coloanal anastomosis (*Fig. 1*) or coloanal J pouch reconstruction (*Fig. 2*), once the surgeon had decided that the patient would undergo low anterior rectal resection. Random allocation was performed by telephone contact with the central study secretariat located in the Department of Surgery of the Würzburg Medical School.

The primary outcome measure was quality of life assessed at predefined, regular intervals. Perioperative and postoperative complications, as well as functional results and anorectal physiology, constituted secondary outcome measures.

All consecutive adult patients with primary cancer of the lower and middle third of the rectum presenting during the study period were included. Written informed consent was obtained from all patients. Patients with manifest or latent faecal incontinence, and patients with guardians or those refusing randomization were excluded from the trial. All comparative analyses were completed on an intention-to-treat basis.

According to a preliminary calculation, a sample size of 90–100 patients was targeted (see below). However, the first results of small randomized trials that reported superior functional results of the pouch–anal reconstruction were published just before the outset of the present study[9,10]. Moreover, in the light of the large randomized trial by Hallböök *et al.*[8], which was published during the early phase of this trial and also showed significant functional benefits in favour of J pouch construction, an interim analysis was planned after recruitment of the first 60 patients. As quality of life with respect to certain domains and functional data were significantly better in the patients with a pouch, the trial was terminated at this point.

Patients and operative procedure

A total of 102 patients with rectal tumours located in the lower third (less than 8 cm from anal verge) and middle third (8–12 cm) were operated during the study period (*Fig. 3*). Of these, 38 patients were excluded from randomization for following reasons: 18 underwent abdominoperineal resection (APR) (total APR rate for all rectal cancers, including those of the proximal third (n = 56), 11 per cent), 12 patients had a transanal excision, three had latent faecal incontinence, two underwent an extended resection owing to synchronous colonic tumours, two had a

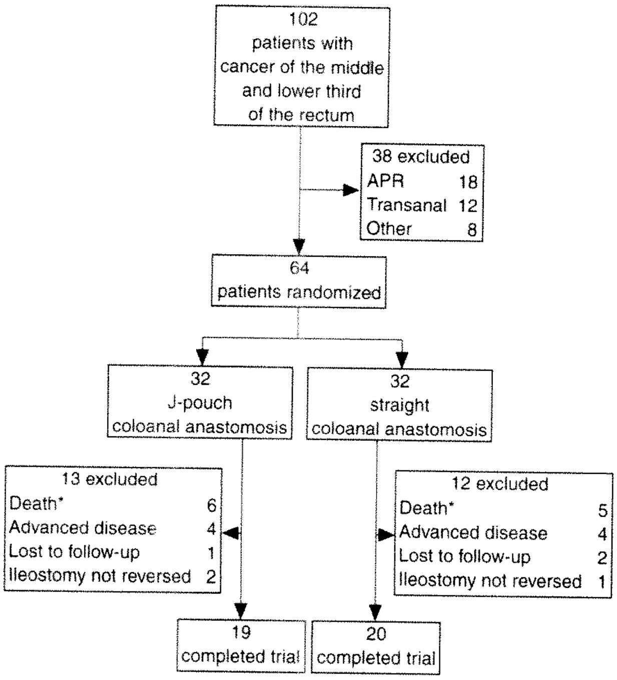

Fig. 3 Study profile. *There were four tumour-related deaths in the pouch group and three in the straight group. APR, abdominoperineal resection

palliative Hartmann's procedure and one patient underwent a palliative colostomy without resection. Sixty-four patients were randomized to either coloanal J pouch reconstruction (n = 32) or straight coloanal anastomosis (n = 32). During the study period 13 patients from the pouch group and 12 patients from the straight group were excluded from further analysis leaving 19 and 20 patients respectively who completed the trial (*Fig. 3*). Generally, patients with either metastatic and/or advanced disease were excluded from further analysis as quality of life in these patients was evidently compromised for reasons not necessarily related to anorectal function.

The operative approach was via a midline abdominal incision. After exploration and high ligation of the inferior mesenteric vessels, the rectum was transected at the level of the levator plane. Total mesorectal excision with preservation of the sacral parasympathetic nerve roots and hypogastric plexus was invariably performed. The left colon and splenic flexure was mobilized completely to ensure a tension-free reconstruction. In the case of a straight coloanal anastomosis the descending colon was anastomosed in an end-to-end fashion to the anal canal using either a circular stapler (n = 28) or a transanal hand suture (n = 4). The colonic pouch was created by folding the descending colon to the form of a 'J', 5–6 cm in length. The septum between the two lumina was transected with a straight stapler device. The pouch was then anastomosed to the anus, using either a circular stapler (n = 29) or hand suture (n = 3). All patients had a defunctioning ileostomy that was reversed after a median of 88 (range 41–196) days. The length of time before the stoma was closed in an individual patient was primarily determined by whether or not adjuvant treatment was added and/or whether anastomotic complications had occurred in the postoperative course.

Table 1 Functional score used to determine faecal continence and related functional variables

	Score
Stool frequency (per day)	
1–2	2
3–5	1
> 5	0
Stool consistency	
Formed	2
Pasty	1
Watery	0
Urge to defaecate	
Normal	2
Uncertain	1
Missing	0
Warning period	
Normal (minutes)	2
Shortened (seconds)	1
Missing	0
Discrimination	
Normal	2
Poor	1
Missing	0
Need for additional anal hygiene	
Never	2
Occasionally	1
Always	0
Soiling	
Not present	6
With stress/diarrhoea	3
Always	0
Incontinence to gas	
Never	6
Occasionally	3
Always	0
Incontinence to liquids	
Never	6
Occasionally	3
Always	0
Incontinence to solids	
Never	6
Occasionally	3
Always	0

0–11, Major incontinence; 12–23, moderate incontinence; 24–30, minor incontinence; 31–36, complete continence

Using a standardized protocol patients were assessed before operation (OP I), at the time of stoma closure

Table 2 Baseline characteristics of the 64 patients included in the trial

	Pouch group (*n* = 32)	Straight group (*n* = 32)	All patients (*n* = 64)
Age (years)*	64(11)	67(9)	65(10)
Women	11	13	24
UICC stage†			
I	15	11	26
II	4	6	10
III	9	8	17
IV	4	5	9
Tumour height above anal verge(cm)*	8·7(2·9)	9·4(2·4)	9·0(2·7)
ASA classification			
I	1	0	1
II	16	23	39
III	13	7	20
IV	2	2	4
Preoperative haemoglobin (g/dl)*	13·5(1·8)	13·6(1·6)	13·6(1·8)
Preoperative haematocrit (%)*	40·1(5·2)	40·0(4·8)	40·0(4·9)
Preoperative albumin (g/dl)*	4·4(0·6)	4·2(0·7)	4·3(0·7)
Postoperative radio/chemotherapy	6	5	11

*Values are means(s.d.). †Two patients in the straight group had a large recurrent adenoma. UICC, Union Internacional Contra la Cancrum. ASA, American Society of Anesthesiologists. There were no significant differences between the two groups

Table 3 Intraoperative and early postoperative course

	Pouch group (*n* = 32)	Straight group (*n* = 32)	All patients (*n* = 64)
Operating time (min)	324(87)	299(98)	312(94)
Transfusion requirements*	3·4(2·5)	2·9(1·6)	3·0(2·0)
Time spent in ICU (days)	2·1(1·5)	3·9(7·0)	3·0(5·3)
First bowel movement (days)	2·5(1·4)	3·0(1·3)	3·0(1·4)

Values are means(s.d.). *Units of packed cells. ICU, intensive care unit. There were no significant differences between the two groups

(OP II), and at 3, 6, 9 and 12 months after stoma closure. Apart from routine oncological follow-up, the study-specific 3-monthly evaluation included measurement of quality of life, standardized scoring of the functional results and anorectal manometry.

Quality of life measurement

Quality of life was measured using three different instruments: the Gastrointestinal Quality of Life Index (GIQLI)[19], the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30[20] and the EORTC colorectal module QLQ-CR38[21]. The first two instruments represent generic tools and can be applied to a wide range of disease entities (the GIQLI for all patients with benign and/or malignant gastrointestinal disorders, and the EORTC QLQ-C30 for all patients with malignant tumours), while the EORTC QLQ-CR38 is specifically for the evaluation of patients with colorectal cancer.

The GIQLI by Eypasch *et al.*[19] comprises 36 multidimensional items covering symptoms, and physical, emotional and social dysfunction related to gastrointestinal diseases or their treatments. Each item scores from 0 to 4 points. The GIQLI is calculated by simple addition of all item scores so that an overall score of 0 would constitute the worst, while a score of 144 represents the best possible result. Furthermore, each dimension can be analysed separately.

Data analysis for the EORTC instruments was carried out using the official scoring procedures for the QLQ-C30 and QLQ-CR38. The QLQ-C30 includes five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales and six single items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties), as well as a global health status/quality of life scale. In both the QLQ-C30 and the QLQ-CR38 each functional scale ranges from 0 to 100, with a higher score representing a higher level of functioning and therefore a better quality of life. The symptom scales are also transformed such that all scales/items range from 0 to 100. However, higher scores represent a higher level of

Table 4 Postoperative complications during hospital stay

	Pouch group (n = 32)	Straight group (n = 32)	All patients (n = 64)
Death	2	0	2
Symptomatic anastomotic leak	3	4	7
Haemorrhage	0	1	1
Small bowel obstruction	1	0	1
Severed ureter	0	1	1
Sepsis	1	1	2
Wound infection	2	2	4
Cardiopulmonary	2	3	5
Urinary infection	1	2	3
Deep vein thrombosis	0	1	1
Relaparotomy	2	1	3

symptomatology which in turn reflects poorer quality of life.

The EORTC QLQ-CR38 comprises 38 questions which include a total of four functional scales/items: body image, sexual functioning, sexual enjoyment and future perspective. Furthermore, it includes a number of multi-item scales and single items assessing a variety of symptoms associated with colorectal cancer: radiotherapy side-effects on micturition, chemotherapy side-effects, general symptoms in the gastrointestinal area, sexual dysfunction in men, sexual dysfunction in women, problems with defaecation, stoma-related problems and weight loss.

Functional score

Anorectal function was assessed using a standardized scoring system that allows the precise evaluation of various important functional subqualities which together constitute anorectal function and faecal continence (*Table 1*).

Anorectal manometry

All manometry was performed using a perfused low-compliance capillary system (Arndorfer, Greendale, Wisconsin, USA). Details of the technique used have been published recently[22]. The following variables were measured: sphincter length, resting pressure, maximum squeeze pressure, relaxation of the internal anal sphincter (RIAS), rectal compliance and vector volume.

Statistical analysis

Sample size analysis was performed based on the assumption that a difference in quality of life for the GIQLI or the domain 'global health status/quality of life' of the EORTC QLQ-C30 of 60 per cent of the standard deviation was significant, i.e. for the GIQLI a difference of 9 points given a standard deviation of 15. For $P < 0.05$ and a power of 0·8, a sample size of 45 per group would be required for a two-tailed test with unpaired data.

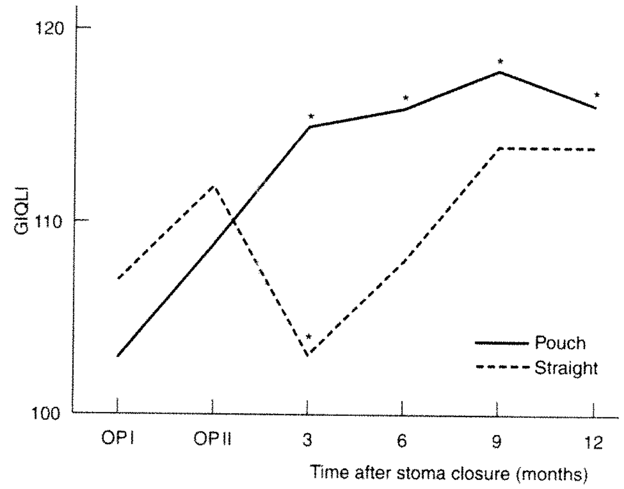

Fig. 4 Mean Gastrointestinal Quality of Life Index (GIQLI) for patients with a pouch or straight coloanal anastomosis. OP I, before the primary operation; OP II, time of stoma closure. $^*P < 0.05$ *versus* OP I (paired Wilcoxon test)

Data are reported as mean(s.d.). Fisher's exact test was used to compare proportions and Mann–Whitney U test to compare continuous data. Longitudinal data within a single group were evaluated with the paired Wilcoxon test. For all analyses $P < 0.05$ was considered significant.

Results

Patient characteristics and postoperative complications

Characteristics, including oncological data, of the 64 patients within the trial are listed in *Table 2*. Baseline characteristics were similar in the two groups, both for the complete cohort (n = 64) and the patients (n = 39) who completed the trial. Details of the perioperative course are shown in *Table 3*, while postoperative complications are summarized in *Table 4*; for both cohorts (n = 64 and n = 39) there were no significant differences between patients who had a straight or pouch coloanal anastomosis.

Quality of life

Gastrointestinal Quality of Life Index

The longitudinal profiles for each group differed significantly. The GIQLI increased steadily in the pouch group resulting in a significantly better quality of life at 3 months ($P = 0.03$), 6 months ($P = 0.05$), 9 months ($P = 0.03$) and

Table 5 Gastrointestinal Quality of Life Index and dimensions before operation, at the time of stoma reversal, and 3, 6, 9 and 12 months thereafter

	Pouch group	Straight group	*P**
GIQLI (0–144)			
OP I	103(12)	107(21)	0·19
OP II	109(17)	112(17)	0·53
3 months	115(12)	103(21)	0·09
6 months	116(17)	108(15)	0·19
9 months	118(14)	114(17)	0·69
12 months	116(21)	114(18)	0·85
Symptoms (0–76)			
OP I	62(7)	61(10)	0·94
OP II	66(7)	68(6)	0·36
3 months	63(7)	58(8)	0·06
6 months	64(8)	59(6)	0·06
9 months	64(7)	62(6)	0·47
12 months	62(8)	62(9)	0·84
Psychological well-being (0–20)			
OP I	9(3)	11(4)	0·12
OP II	13(3)	13(4)	0·91
3 months	15(3)	14(5)	0·21
6 months	15(3)	15(3)	0·44
9 months	15(3)	15(4)	0·81
12 months	15(3)	5(4)	0·76
Physical functioning (0–28)			
OP I	19(5)	19(6)	0·60
OP II	17(5)	18(5)	0·62
3 months	21(4)	18(6)	0·08
6 months	21(5)	19(5)	0·58
9 months	21(4)	21(6)	0·55
12 months	20(5)	20(5)	0·81
Social functioning (0–16)			
OP I	12(3)	13(4)	0·06
OP II	10(4)	10(4)	0·88
3 months	13(3)	11(4)	0·20
6 months	12(3)	12(3)	0·89
9 months	13(2)	13(3)	0·85
12 months	13(2)	13(3)	0·35
Medical treatment (0–4)			
OP I	1·8(1·2)	2·9(1·2)	0·009
OP II	2·7(1·0)	3·0(1·3)	0·26
3 months	3·5(0·6)	2·9(0·9)	0·03
6 months	3·4(0·9)	3·2(0·9)	0·28
9 months	3·7(0·6)	3·4(1·0)	0·58
12 months	3·5(0·6)	3·4(0·8)	0·89

Values are mean(s.d.). The highest and lowest score for each variable is indicated. GIQLI, Gastrointestinal Quality of Life Index; OP I, before operation; OP II, at the time of stoma reversal. *Mann–Whitney *U* test

Table 6 Global health status and functional scales measured with the European Organization for Research and Treatment of Cancer QLQ-C30 before operation, at the time of stoma reversal, and 3, 6, 9 and 12 months thereafter

Functional scales	Pouch group	Straight group	*P**
Global health status/quality of life			
OP I	54(20)	55(25)	0·71
OP II	67(20)	60(18)	0·27
3 months	74(17)	57(24)	0·04
6 months	76(18)	62(19)	0·02
9 months	74(19)	66(19)	0·42
12 months	78(14)	66(18)	0·04
Physical functioning			
OP I	94(12)	92(16)	0·87
OP II	77(22)	81(21)	0·64
3 months	88(15)	85(19)	0·68
6 months	87(17)	87(17)	0·93
9 months	92(13)	88(16)	0·47
12 months	93(12)	90(16)	0·76
Role functioning			
OP I	78(29)	81(29)	0·74
OP II	51(36)	53(32)	0·91
3 months	67(30)	64(31)	0·80
6 months	79(28)	68(32)	0·24
9 months	81(23)	74(21)	0·26
12 months	73(27)	72(34)	0·75
Emotional functioning			
OP I	51(25)	59(30)	0·32
OP II	58(24)	64(28)	0·42
3 months	75(18)	62(31)	0·16
6 months	79(20)	72(27)	0·52
9 months	73(19)	77(27)	0·36
12 months	82(15)	76(29)	1·00
Cognitive functioning			
OP I	81(29)	87(18)	0·92
OP II	83(23)	86(22)	0·41
3 months	86(17)	81(23)	0·61
6 months	90(16)	82(22)	0·18
9 months	88(16)	90(13)	0·88
12 months	88(20)	84(19)	0·43
Social functioning			
OP I	79(27)	83(28)	0·44
OP II	65(36)	73(32)	0·53
3 months	87(15)	68(32)	0·09
6 months	87(17)	78(29)	0·49
9 months	88(19)	79(28)	0·42
12 months	80(29)	83(27)	0·80

Values are mean(s.d.). Values range from 0 (poor quality of life) to 100 (excellent quality of life). OP I, before operation; OP II, at the time of stoma reversal. *Mann–Whitney *U* test

12 months ($P = 0{\cdot}02$) compared with the preoperative level (*Fig. 4*). In contrast, the index declined significantly ($P = 0{\cdot}02$) after the reversal of ileostomy (OP II) in the straight group, indicating a substantial decrease in quality of life at 3 months compared with the OP I and OP II level (*Fig. 4*).

Comparing the two groups, it is noteworthy that the overall index as well as the scores for the various dimensions were inferior in the pouch group at the beginning of the observation period (OP I) but the situation was reversed at 3 months (*Table 5*).

QLQ-C30

With reference to the cardinal domain 'global health status/quality of life' significantly better results were observed for the pouch group at 3 months ($P = 0{\cdot}04$), 6 months

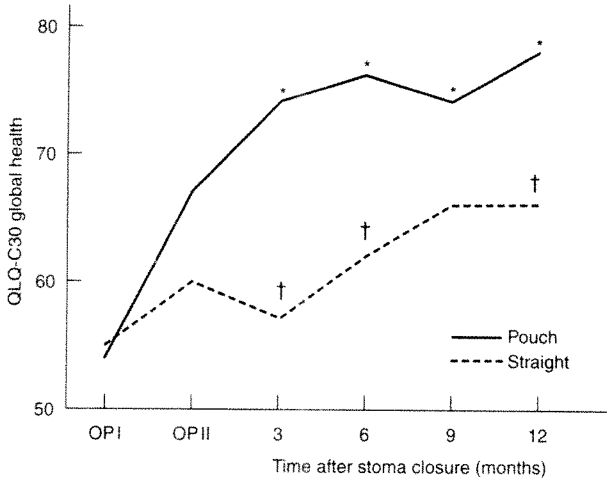

Fig. 5 Mean score in the domain 'global health status/quality of life' in the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire for patients with a pouch or straight coloanal anastomosis. OP I, before the primary operation; OP II, time of stoma closure. $^*P < 0.05$ *versus* OP I (paired Wilcoxon test); $^†P < 0.05$ *versus* pouch group (Mann–Whitney U test)

($P = 0.02$) and 12 months ($P = 0.04$) after stoma closure when compared with the straight group (*Fig. 5*). Intragroup analysis showed a much steeper increase of this domain in the pouch group with significantly better quality of life at 3 months ($P = 0.03$), 6 months ($P = 0.02$), 9 months ($P = 0.03$) and 12 months ($P = 0.003$) compared with the preoperative level, while this domain never improved significantly in the straight group. Results of all domains are specified in *Table 6*.

QLQ-CR38

The disease-specific tool QLQ-CR38 also showed poorer results for patients with a pouch in virtually all domains at the beginning of the trial, albeit only at a statistically relevant level for the domain 'body image' ($P = 0.03$). Again, this trend was completely reversed 3 months after stoma closure. The symptom scale 'defaecation problems' differed significantly at 3 months ($P = 0.003$) indicating more problems in patients with a straight coloanal anastomosis (*Table 7*).

Table 7 All functional scales and certain symptom scales measured with the European Organization for Research and Treatment of Cancer QLQ-CR38 before operation, at the time of stoma reversal, and 3, 6, 9 and 12 months thereafter

	Pouch group	Straight group	*P**
Functional scales			
Body image			
OP I	74(20)	87(20)	0·03
OP II	68(25)	68(24)	1·00
3 months	78(16)	71(25)	0·39
6 months	79(20)	81(23)	0·59
9 months	83(19)	78(21)	0·44
12 months	70(21)	80(17)	0·15
Sexual functioning			
OP I	25(25)	30(30)	0·66
OP II	26(26)	23(27)	0·54
3 months	31(27)	22(22)	0·33
6 months	32(25)	26(28)	0·50
9 months	31(29)	29(28)	0·82
12 months	42(35)	32(30)	0·36
Sexual enjoyment			
OP I	62(23)	57(32)	0·79
OP II	52(24)	42(30)	0·52
3 months	45(39)	37(26)	0·68
6 months	67(22)	46(18)	0·06
9 months	67(27)	52(30)	0·37
12 months	67(31)	43(23)	0·06
Future perspective			
OP I	10(20)	28(35)	0·08
OP II	38(35)	35(36)	0·74
3 months	58(31)	52(41)	0·63
6 months	63(38)	59(35)	0·68
9 months	49(33)	58(33)	0·44
12 months	67(31)	65(31)	0·79
Symptom scales			
Symptoms in the gastrointestinal area			
OP I	19(17)	17(15)	0·72
OP II	12(14)	10(15)	0·52
3 months	17(13)	21(21)	0·86
6 months	13(11)	17(14)	0·48
9 months	16(18)	14(13)	0·94
12 months	22(24)	14(15)	0·51
Defaecation or stoma (OP II) problems			
OP I	23(11)	22(20)	0·30
OP II	35(21)	33(21)	1·00
3 months	21(12)	39(20)	0·003
6 months	22(16)	36(19)	0·06
9 months	21(14)	28(20)	0·24
12 months	23(21)	26(19)	0·56

Values are mean(s.d.). Values in functional scales range from 0 (poor quality of life) to 100 (excellent quality of life); those in symptom scales range from 0 (excellent quality of life) to 100 (poor quality of life). OP I, before operation; OP II, at the time of stoma reversal. *Mann–Whitney U test

Functional score

The overall score differed significantly between the two groups 3 months after stoma reversal ($P = 0.04$). *Fig. 6* shows the change in score for the pouch group which was only significantly worse initially ($P = 0.04$, OP I *versus* 3 months) while patients with a straight anastomosis had a

Table 8 Overall functional score and certain functional subqualities before operation, and 3, 6, 9 and 12 months after ileostomy reversal

Functional scores	Pouch group	Straight group	P^*
Overall score			
OP I	33(4)	35(2)	0·23
3 months	32(4)	28(6)	0·04
6 months	32(4)	29(4)	0·09
9 months	32(5)	31(4)	0·56
12 months	32(6)	32(3)	0·69
Stool frequency			
OP I	1·8(0·6)	2·0(0·0)	0·04
3 months	1·2(0·7)	1·2(1·5)	0·56
6 months	1·0(0·8)	1·0(0·8)	1·00
9 months	1·4(0·6)	1·2(0·8)	0·57
12 months	1·3(0·7)	1·3(0·7)	0·93
Urge to defaecate			
OP I	2·0(0·0)	2·0(0·0)	1·00
3 months	1·9(0·2)	1·9(0·2)	1·00
6 months	1·9(0·2)	1·9(0·3)	0·93
9 months	2·0(0·0)	2·0(0·0)	1·00
12 months	1·9(0·2)	2·0(0·0)	0·38
Warning period			
OP I	2·0(0·2)	2·0(0·0)	0·34
3 months	1·9(0·2)	1·7(0·5)	0·03
6 months	1·9(0·2)	1·7(0·5)	0·04
9 months	2·0(0·2)	1·8(0·4)	0·07
12 months	1·9(0·2)	1·9(0·3)	0·96
Need for additional anal hygiene			
OP I	1·8(0·4)	1·8(0·4)	1·00
3 months	1·6(0·5)	1·3(0·5)	0·07
6 months	1·6(0·6)	1·3(0·4)	0·02
9 months	1·8(0·4)	1·5(0·5)	0·11
12 months	1·5(0·6)	1·6(0·5)	0·84
Soiling			
OP I	5·4(1·2)	5·6(1·1)	0·70
3 months	4·7(1·5)	3·5(1·5)	0·02
6 months	5·1(1·7)	4·0(1·4)	0·03
9 months	5·3(1·3)	4·8(1·5)	0·39
12 months	4·8(1·9)	4·8(1·5)	0·91
Incontinence to gas			
OP I	5·1(1·7)	5·7(0·9)	0·21
3 months	5·1(1·4)	4·7(1·5)	0·44
6 months	4·9(1·8)	4·9(1·7)	1·00
9 months	5·1(1·8)	5·0(1·9)	0·94
12 months	5·3(1·7)	5·2(1·4)	0·64

Values are mean(s.d.). Overall values range from 0 (complete incontinence) to 36 (perfect continence). For scores of subqualities see *Table 1*; generally, higher scores delineate better function. OP I, before operation. *Mann–Whitney *U* test

more marked decrease in anorectal function. In fact, after 3 and 6 months differences were highly significant ($P < 0{\cdot}001$) compared with OP I, and remained significant after 9 months ($P = 0{\cdot}007$) and 12 months ($P = 0{\cdot}02$). There were significant differences between the two groups with regard to warning period, soiling and need for hygienic care (*Table 8*).

Table 9 Anorectal manometry data before operation, at the time of stoma reversal, and 3, 6, 9 and 12 months thereafter

	Pouch group	Straight group	P^*
Resting pressure (mmHg)			
OP I	90(26)	86(33)	0·45
OP II	64(21)	69(33)	1·00
3 months	64(21)	64(30)	0·83
6 months	62(23)	64(20)	0·78
9 months	63(18)	68(19)	0·50
12 months	55(23)	68(36)	0·25
Squeeze pressure (mmHg)			
OP I	106(86)	99(63)	0·92
OP II	118(56)	108(73)	0·37
3 months	118(58)	108(77)	0·61
6 months	110(61)	122(76)	0·68
9 months	120(60)	105(64)	0·49
12 months	116(47)	109(74)	0·34
Rectal compliance (ml/mmHg)			
OP I	2·6(1·9)	2·0(0·8)	0·17
OP II	3·1(1·1)	2·6(0·9)	0·09
3 months	3·5(1·4)	2·9(1·2)	0·21
6 months	3·6(1·5)	2·7(1·4)	0·09
9 months	3·2(1·1)	3·3(1·5)	0·80
12 months	3·1(1·4)	3·1(1·8)	0·79

Values are mean(s.d.). OP I, before operation; OP II, at the time of stoma reversal. *Mann–Whitney *U* test

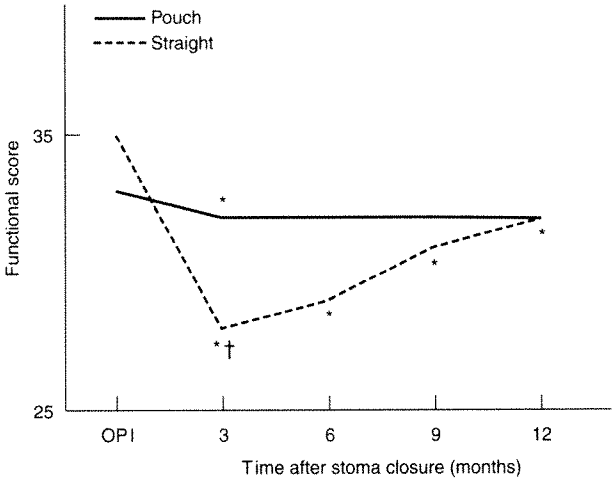

Fig. 6 Mean anorectal functional score for patients with a pouch or straight coloanal anastomosis. OP I, before the primary operation. $^*P < 0{\cdot}05$ *versus* OP I (paired Wilcoxon test). $^\dagger P < 0{\cdot}05$ *versus* pouch group (Mann–Whitney *U* test)

Anorectal manometry

Table 9 summarizes the data for resting pressure, squeeze pressure and rectal compliance. Although there was a trend towards better neorectal compliance in patients with a pouch in the early postoperative period, this did not reach statistical significance. All other variables, including sphincter length, RIAS and vector volume measurements, did not differ between the groups.

Discussion

A substantial proportion of patients undergoing surgery for rectal cancer may experience a wide range of problems affecting their physical, psychological, social and emotional functioning. Many disturbances are closely related to physical disabilities such as disturbed sexual, urinary and bowel function. While the occurrence and incidence of these complications is well documented in the literature, the impact of functional deficiencies on the overall quality of life is poorly understood. A recent literature review by Camilleri-Brennan and Steele[23] on quality of life after treatment for rectal cancer concluded that many studies had methodological shortcomings. In fact, only three reports (two from the same institution) in the English language literature have formally described quality of life measurement in all its dimensions after surgery for rectal cancer[15,24,25]. All studies used the Nottingham Profile which, as a generic questionnaire, may not be sensitive enough to measure changes in quality of life in these patients who may exhibit a rather specific functional symptomatology[15,21]. Moreover, there is a general lack of longitudinal studies that have assessed quality of life in patients with colorectal cancer[26].

The only study that measured quality of life in patients randomized to either straight or pouch reconstruction, and failed to detect differences between the two groups, did not use any disease- or organ-specific instrument[15]. In addition, it only measured quality of life 1 year after surgery. However, most published data[27–29] show that functional deficiencies improve over time and that late outcome is often reasonably good, even in patients with a straight coloanal anastomosis, which is in keeping with the present results. Adaptation phenomena are well known in patients adjusting to functional deficiencies and result in a better quality of life than might be expected from their functional results[30,31]. It is therefore assumed that any differences detected at a statistically significant level must be of a rather profound nature which also means of major clinical relevance. The principal finding in this respect was the significantly superior scoring of patients with a pouch in the domain ‘global health status/quality of life’. This highly relevant but non-specific finding may be further analysed by examining the various domains of all the instruments used and by interpreting the results of the functional score. It then becomes apparent that quality of life in these patients is closely related to functional qualities such as warning period before defaecation, soiling, hygienic care needed and requirement for medical treatment.

The present report is among the first studies in the field of colorectal surgery to analyse systematically the relationship between functional results and quality of life. It was demonstrated that better anorectal function does translate into better quality of life. In this context it is important to employ instruments that are sensitive enough to detect differences and to measure early in the postoperative course before incipient adaptation occurs. The results of the interim analysis together with the data emerging in the literature, which continue to demonstrate the functional superiority of the pouch procedure, convinced the authors to discontinue the study as it was deemed unethical to withhold pouch reconstruction if indicated and technically feasible. Furthermore, neither perioperative morbidity, especially with regard to anastomotic complications, nor operating time were increased in the pouch procedure. In fact, the largest randomized trial on this topic showed a significantly reduced rate of anastomotic dehiscence in the pouch group[8]. It may be argued that the advantages of the J pouch are only transient and disappear towards the end of the first year after operation, but one must take into account that a substantial proportion of patients might not be alive 1–2 years after operation owing to the nature of the disease. Unquestionably, for these patients good functional results and, more importantly, the best possible quality of life in the immediate postoperative phase are fundamental.

In summary, this randomized trial provides strong evidence that patients undergoing low anterior rectal resection and coloanal J pouch reconstruction may not only expect better functional results but also an improved quality of life in the early months after surgery compared with patients who receive a straight coloanal anastomosis. Apart from the occasional patient in whom pouch construction is not possible technically, this method of reconstruction should clearly be given preference over the traditional technique of end-to-end anastomosis.

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Long-term outcome of hepaticojejunostomy with routine access loop formation following iatrogenic bile duct injury

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Background: Hepaticojejunostomy is the 'gold standard' procedure for repairing iatrogenic bile duct injuries. The aim of this study was to examine the long-term outcome following hepaticojejunostomy for iatrogenic bile duct injury and the utility of routine construction of an access loop.
Methods: Patients with iatrogenic biliary injuries were treated with hepaticojejunostomy and access loop by a single surgeon. Injuries were classified according to the Bismuth level. An 'excellent' outcome was achieved if the patient never experienced jaundice or cholangitis in the follow-up period, and the outcome was 'good' if the patient developed symptoms but was asymptomatic for more than 12 months.
Results: Forty-eight patients underwent such operation. There was one operative death. Thirty-three patients were followed for 3 years or more (mean follow-up 80·4 (range 46–118) months). Thirteen of the 33 injuries were Bismuth level II, 13 were Bismuth level III and seven were Bismuth level IV. Outcome was dependent on the Bismuth level ($P < 0.001$). It was excellent in all 13 patients with Bismuth level II injuries, excellent in seven and good in six of the 13 patients with Bismuth level III injuries, and excellent in one and good in six of the seven patients with Bismuth level IV injuries. Moreover, the need for access loop intervention was dependent on the Bismuth level ($P < 0.001$). No patient with Bismuth level II injury required intervention, compared with five of 13 with Bismuth level III and six of seven with Bismuth level IV injuries.
Conclusion: Biliary reconstruction affords satisfactory long-term outcome. The likelihood of needing the access loop for radiological intervention is dependent on the Bismuth level. The authors recommend that an access loop be constructed in all patients with Bismuth level III and IV injuries.

Paper accepted 29 April 2002

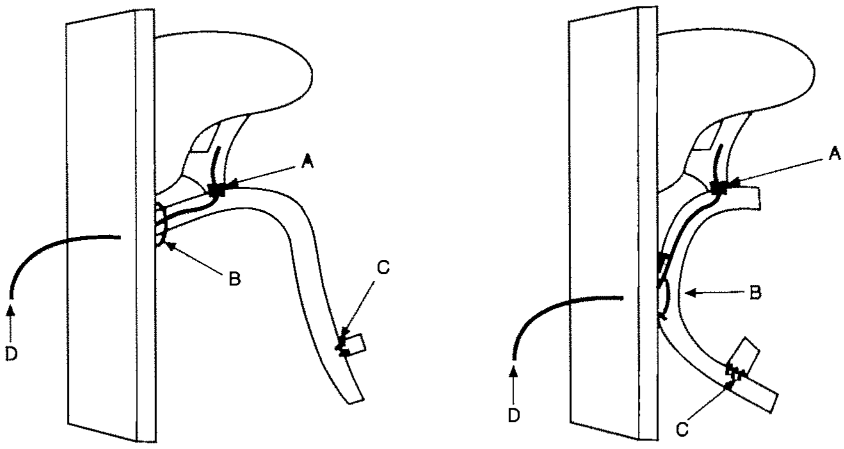
British Journal of Surgery 2002, **89**, 1118–1124

Introduction

Roux-en-Y hepaticojejunostomy is the standard procedure used by most biliary surgeons to repair iatrogenic strictures[1], and reported series have shown good outcome after these operations[2–4]. However, cholangitis, recurrent anastomotic strictures and hepatodocholithiasis, which account for the majority of long-term complications following this procedure, can result in liver cirrhosis and portal hypertension if left untreated[5,6].

Although many of these long-term complications may be treated by means of interventional radiology without the need for reoperation, transhepatic manipulations can be difficult and are prone to complications. The provision of an 'access loop' may facilitate such interventions by allowing intubation via the jejunum[7,8]. The end of the afferent limb of the Roux-en-Y can be placed in a subcutaneous or subparietal position and its position marked with radio-opaque markers at the time of the biliary reconstruction procedure (*Fig. 1*). This allows access to the biliary tree by the interventional radiologist at a later date, enabling dilatation of strictures and the percutaneous extraction of calculi without the need for transhepatic intubation with its associated morbidity. The use of such an access loop has been shown to be a useful adjunct in managing complications in these patients[8,9]. Whether an access loop should be used in all cases of biliary–enteric anastomosis is unclear: some surgeons use it selectively, others in every patient.

In this study the long-term outcome after hepaticojejunostomy for iatrogenic strictures was examined in patients who were followed for more than 3 years. The utility of routine access loop formation in these patients was also examined in order to identify features that might predict



a Type I **b** Type II

Fig. 1 Hepaticojejunostomy with the two different types of access loop: a type I; b type II. A, hepaticojejunostomy; B, point of attachment of access loop with a circular steel marker; C, jejunojejunal anastomosis; D, exteriorized infant feeding tube for subsequent cholangiography

those who will require its formation at the time of hepaticojejunostomy.

Patients and methods

This was a retrospective analysis of a prospective database of 48 patients who underwent hepaticojejunostomy with routine access loop formation following iatrogenic injury at cholecystectomy. The operations were performed by one surgeon between December 1990 and April 2000 at the authors' institution.

Bile duct injuries were classified after Bismuth[10]: injuries more than 2 cm from the confluence of the hepatic ducts were classed as Bismuth level I, those less than 2 cm from the confluence as Bismuth level II, those involving the confluence as Bismuth level III, and those in which continuity between the right and left hepatic ducts was lost as Bismuth level IV.

The operative procedure involves exposing the hilum and lowering the hilar plate, if necessary, to gain access to the left hepatic duct. The stricture is then resected back to a normal duct with healthy mucosa. The jejunum is divided 10–20 cm from the ligament of Treitz and the distal end is brought in a retrocolic position as a Roux limb (70 cm in length). The biliary–enteric anastomosis is constructed end to side with 4/0 polydioxanone. The end of the 10–cm access loop is fixed to the parietal peritoneum to the right side and marked with a circular steel suture as a radiological marker for future use as an access loop. This is the preferred method of constructing an access loop as it is easier for the radiologist to use, and the present authors have designated this a type I loop. In a type II access loop, the jejunal loop is attached to the parietal peritoneum at a point distal to the biliary–enteric anastomosis. This latter configuration is necessary in some patients undergoing revisional biliary–enteric anastomosis and in those whose body habitus does not allow for a type I loop configuration (*Fig. 1*). It is the authors' usual practice to place a 5-Fr infant feeding tube across the anastomosis; this is brought out through the fixed end of the access loop and is removed 1 week after operation, once cholangiography has been performed to assess the anastomosis (*Fig. 2*).

Follow-up consisted of hepatic scintigraphy with an iminodiacetic acid (HIDA) scan at 3 months and liver function tests at 3, 6 and 12 months, and yearly thereafter. Patients who reported jaundice or symptoms suggestive of cholangitis were investigated with HIDA scanning followed by cholangiography, using the access loop to demonstrate the biliary anatomy and to identify and dilate strictures or extract calculi as necessary. Mild derangement of liver function alone was not regarded as an indication for cholangiography via the access loop.

The clinical outcome was assessed as defined previously[2]. Outcome was defined as 'excellent' if the patient never had jaundice or cholangitis, 'good' if the patient developed jaundice or cholangitis at some time during follow-up but

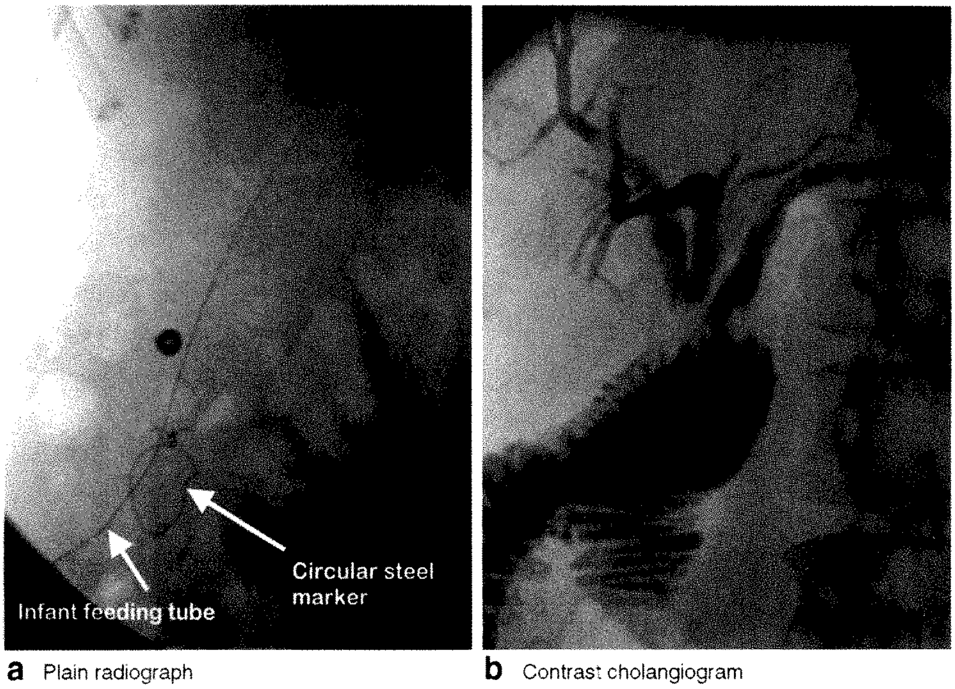


Fig. 2 Immediate postoperative cholangiography using the access loop. **a** Plain radiograph. **b** Contrast cholangiogram demonstrating the hilar anastomosis and the end of the infant feeding tube in the left hepatic duct

was symptom-free for longer than 12 months after access loop intervention, or 'poor' if at the time of follow-up the patient did not satisfy the above criteria.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 10·1 (SPSS, Chertsey, UK). Continuous data were compared using parametric and non-parametric tests as appropriate. Proportions were compared with the χ^2 and Fisher's exact test as appropriate. Kaplan–Meier survival curves were used to determine the probability of requiring access loop intervention, and the log rank test was employed to compare medians for different groups.

Results

Patient details

Forty-eight patients underwent hepaticojejunostomy with routine formation of an access loop. The mean age was 50·0 (range 23–80) years, and 37 of the patients were women. The iatrogenic injury was sustained at laparoscopic cholecystectomy (LC) in 32 patients and at open cholecystectomy (OC) in 16. Patients who sustained injury at LC were younger than those who were injured at open operation (mean age 46·7 *versus* 56·8 years; $P = 0.014$, independent sample t test). Forty patients were referred from the UK, seven from abroad and one from the authors' institution.

The injury was recognized at the time of operation in nine of 31 patients (data unavailable for one patient) in the LC group, and in five of 13 (data unavailable for three patients) in the OC group. Intraoperative cholangiography had been performed in three of 22 patients (data unavailable for ten patients) in the LC group, and in two of five (data unavailable for 11 patients) in the OC group. At operation, of the 46 injuries, 16 were found to be Bismuth level II, 20 were Bismuth level III and ten Bismuth level IV.

Following the iatrogenic injury, 23 patients had further non-operative treatments before referral and 14 underwent biliary–enteric anastomosis before referral (*Fig. 3*).

The interval from when the injury was sustained to reconstruction at the authors' institution was shorter in the LC than in the OC group (median 3·2 (range 0–60) *versus* 65·0 (range 0–204) months; $P < 0.001$, Mann–Whitney U test).

Management

Thirty-four reconstructions were primary and 14 followed previous biliary–enteric anastomosis. A type I access loop was constructed in 44 patients and a type II loop in four. The median hospital stay was 14·0 (range 8–93) days. Complications occurred in 13 patients: wound infection

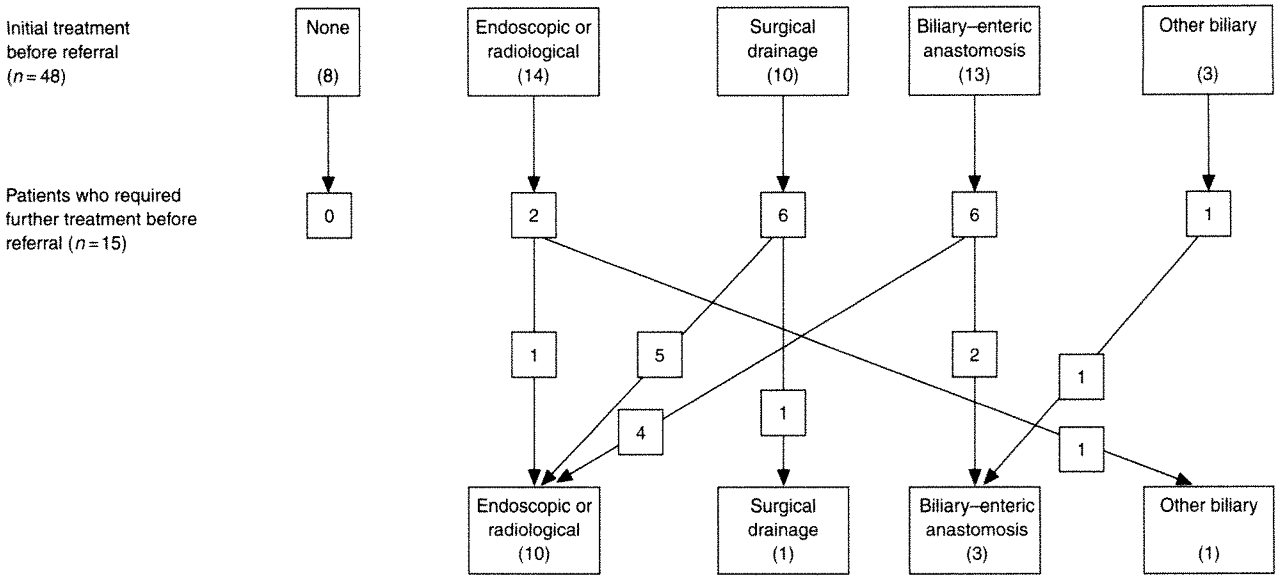

Initial treatment before referral (n=48)
None (8)
Endoscopic or radiological (14)
Surgical drainage (10)
Biliary–enteric anastomosis (13)
Other biliary (3)
Patients who required further treatment before referral (n=15)
0
2
6
6
1
1
5
2
1
4
1
1
Endoscopic or radiological (10)
Surgical drainage (1)
Biliary–enteric anastomosis (3)
Other biliary (1)

Fig. 3 Treatment received by 48 patients before referral for hepaticojejunostomy

in four, anastomotic leak in three, pulmonary infection in two, and one of each of adult respiratory distress syndrome, incisional hernia, haematemesis and back pain.

There was one operative death, and one patient was lost to long-term follow-up. The patient who died had established secondary biliary cirrhosis with portal hypertension and significant ischaemic heart disease, and all attempts at managing repeated attacks of cholangitis conservatively had failed.

Follow-up and outcome

Thirty-three patients were followed for more than 3 years and were used in all subsequent analyses. The characteristics of this group did not differ from those of the group as a whole. The mean length of follow-up for this group was 80·4 (range 46–118) months, with 32 patients being followed for more than 4 years. Thirteen of the 33 patients had Bismuth level II, 13 had Bismuth level III and seven Bismuth level IV strictures. The outcome after operation was excellent in 21 patients and good in 12. The length of the symptom-free period (time since last attack of cholangitis) for those with a good outcome, at the time of follow-up, was a mean of 62·4 (range 17–104) months. All but one patient were symptom-free for longer than 2 years at follow-up.

There was a strong correlation between outcome and the Bismuth level of the injury: a higher injury adversely affected the outcome ($P < 0·001$, two-sided Spearman correlation coefficient) (*Fig. 4*). However, there was no correlation between previous biliary repair and outcome ($P = 0·57$).

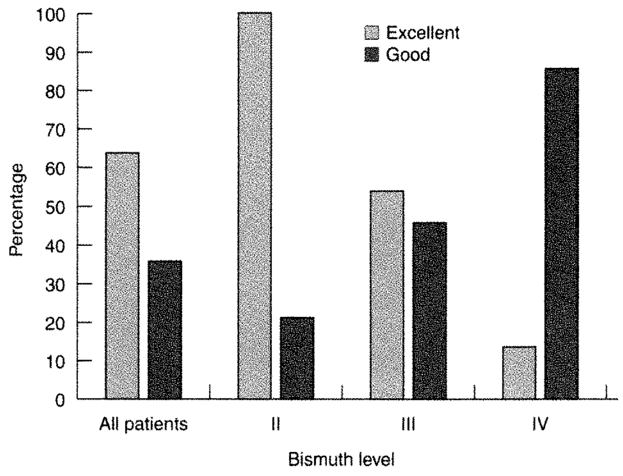


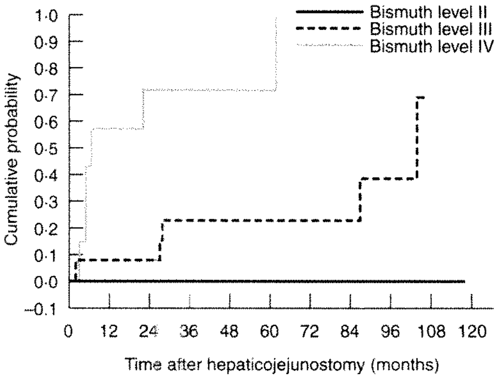
Fig. 4 Outcome stratified by Bismuth level in patients followed for more than 3 years

Use of the access loop

Of the 33 patients, 11 had access loop cholangiography because of symptoms suggestive of recurrent cholangitis or obstructive jaundice. Of these, six required instrumentation via the access loop once, four required it twice and one required it five times. There was a correlation between the Bismuth level of injury and the need for access loop instrumentation; interventions were carried out in six of seven patients with Bismuth level IV injury, in five of 13 with Bismuth level III and in none of the 13 patients with Bismuth level II injury ($P < 0{\cdot}001$, two-sided Spearman correlation coefficient).

Eight patients were found at access loop cholangiography to have strictures that required dilatation, and one patient who had a stricture with intrahepatic stones underwent dilatation and stone extraction. Two patients who were investigated extensively for abdominal pain had a normal finding on access loop cholangiography. Cholangiography via the access loop failed in one patient, who subsequently had transhepatic instrumentation.

Most patients with Bismuth level IV injury required access loop instrumentation within 2 years of operation (median 6·7 (95 per cent confidence interval (c.i.) 2·3 to 11·2) months). However, most patients with Bismuth level III injury who required access loop intervention did so more than 2 years after the operation, at a median of 104·0 (95 per cent c.i. 78·8 to 129·2) months ($P < 0{\cdot}003$, log rank test) (*Fig. 5*).



No. at risk											
Bismuth level II	13	13	13	13	13	13	13	13	13	13	13
Bismuth level III	13	12	12	10	10	8	7	5	2	0	0
Bismuth level IV	7	7	2	2	2	1	0	0	0	0	0

Fig. 5 Cumulative probability of the need for access loop intervention stratified by Bismuth level of injury in patients followed for more than 3 years after hepaticojejunostomy

Discussion

Cholecystectomy is one of the most commonly performed elective general surgical operations. In the 1990s the open procedure was virtually superseded by the laparoscopic approach. This has many advantages over the open approach but has been associated with a two- to threefold increase in the risk of biliary injury, with an estimated incidence of 0·7–0·8 per cent[11–19].

Roux-en-Y hepaticojejunostomy is now the standard procedure for repair of these injuries, and a very good outcome following these operations has been demonstrated in several series[2–4,6].

In this series injury was recognized at the time of operation in about one-third of patients, which is consistent with the findings of other studies[4,5,14,20]. The present authors agree with others that the best outcome for these patients can be achieved in tertiary units. Therefore, the best treatment for injuries recognized during operation is to achieve adequate drainage and to eliminate potential sources of sepsis. The patient can then be transferred to a specialist unit where complete cholangiography, and if necessary angiography, can be achieved before definitive surgery is undertaken. Eradication of sepsis should be attempted in all cases before the repair is performed. Intraoperative cholangiography was performed in a minority of cases, but the role of intraoperative cholangiography in preventing bile duct injuries remains controversial in both open[1,21] and laparoscopic[22–26] cholecystectomy.

The one operative death in this series was that of a 60-year-old patient with a Bismuth level IV injury, with several previous attempts at surgical repair, established portal hypertension and significant cardiovascular disease. Portal hypertension, high injury and previous surgery have been identified as risk factors that adversely affect the outcome in this group of patients[5].

In this series there was no significant disadvantage in outcome when comparing patients who had biliary–enteric anastomosis before referral with those who did not. This is in agreement with other recent data[3], but contrasts with previous experience by the present authors and others[4,5]. This may be due to the increasing experience with these injuries which coincided with the introduction of LC in the 1990s, resulting in early referral to specialist centres[27] and improvements in perioperative management.

The level of the anastomosis in patients who undergo revisional hepaticojejunostomy is always higher than the original injury because further proximal resection of the bile duct is required in order to reach healthy mucosa for anastomosis. The Bismuth level of the injury, amongst other factors, has an important impact on the outcome of these patients[5]. The present authors therefore agree with others that patients should be referred to a specialist centre and attempts at repair outside tertiary units should be discouraged[2,3,6,20,27].

The original description of the access loop involved the fashioning of an enterocutaneous stoma[7]. This was abandoned because of complications associated with the presence of a permanent stoma[28,29]. Subfascial placement of the blind end may also result in parajejunal herniation. In this series the blind end of the access loop was fixed in a subparietal position and marked with a circular steel suture.

The fixation point is placed as laterally as possible, on the right side, in order to reduce the radiation dose to the hands of the radiologist. The authors' experience has shown that good placement and clear marking of the access loop are critical for its usefulness for interventional radiology.

The access loop has been shown to be a useful tool in the management of patients undergoing hepaticojejunostomy[8,9,30–33], and it can be used to remove cholelithiasis and dilate strictures. Although some would advocate its use in all patients, there are no guidelines at present to help surgeons determine when to fashion it selectively in patients with benign strictures[33]. This series suggests that an access loop should be fashioned in all patients with high injuries (Bismuth levels III and IV), because these patients have a 5 in 13 and 6 in 7 chance, respectively, of requiring further intervention.

There was no morbidity associated with the access loop, although one group has reported evidence of bacterial overgrowth resulting in cholangitis, which improved on excising the blind end of the loop[34]. This may have occurred in the presence of a long redundant blind end of the afferent limb. None of the patients in the present series had any evidence of cholangitis in the absence of strictures or calculi; nor did they have gastrointestinal or haematological evidence of small bowel bacterial overgrowth.

In this series three patients developed symptoms and mechanical problems with the anastomosis more than 5 years after the operation (62, 87 and 104 months) (*Fig. 5*), having been perfectly well in the intervening period. The authors therefore recommend extended follow-up of these patients, especially those with higher injuries. It seems adequate to perform annual liver function tests and to allow the patients easy access to outpatient follow-up. Cholangitis is usually a symptom of an underlying mechanical problem – either a stricture or a calculus. A short course of antibiotics may be used to control cholangitis, but every infective episode should be investigated with hepatic scintigraphy and cholangiography through the access loop.

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Original article

Spontaneous tumour rupture and prognosis in patients with hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is a common disease in Taiwan. Ruptured HCC is an uncommon and potentially fatal complication of the condition. Information on the impact of ruptured HCC on hepatic resection is, however, limited.

Methods: The clinical features of 60 patients with ruptured HCC who underwent hepatic resection from 1986 to 1998 were reviewed. Clinical features and factors influencing the outcome of 475 patients with non-ruptured HCC were used for comparison.

Results: Of 535 surgically resected HCCs, 60 (11·2 per cent) were ruptured. Univariate analysis showed that sudden onset of abdominal pain, physical signs of haemodynamic unstability, reduced haemoglobin level and a raised aspartate aminotransferase level were more frequently found in patients with ruptured HCC than in those with non-ruptured tumours. Multivariate stepwise logistic regression analysis revealed sudden-onset abdominal pain to be the only independently significant factor in patients in the ruptured HCC group. The 1-, 3- and 5-year survival rates of patients with non-ruptured HCC were 72·1, 47·3 and 33·9 per cent, and those of patients with ruptured HCC were 54·2, 35·0 and 21·2 per cent respectively. Similar overall survival rates were found in patients with ruptured and non-ruptured HCC, although patients in the non-ruptured HCC group had a significantly better disease-free survival rate ($P = 0.023$).

Conclusion: The presence of sudden-onset abdominal pain is the only independent indicator of ruptured HCC. Hepatic resection, when feasible, is the treatment of choice and can result in an overall survival rate comparable to that of patients with non-ruptured HCC.

Paper accepted 9 May 2002

British Journal of Surgery 2002, 89, 1125–1129

Introduction

Hepatocellular carcinoma (HCC) is a common disease in Taiwan, with an annual age-adjusted incidence of 27·7 per 10^5 population. It is the leading cause of cancer-related death among men and the second cause among women in Taiwan[1].

An uncommon but potentially fatal complication of HCC is spontaneous rupture[2], with a distinct geographical difference in reported incidence ranging from 1 to 22 per cent[3]. When confronted with this life-threatening condition, haemostasis is the primary concern and resection of the tumour is secondary. Hepatic resection is the most effective means of achieving these two goals and, when possible, represents the treatment of choice for ruptured HCC as long-term survival can be achieved in some patients[4–6]. Reports of the outcome of resection for ruptured HCC in terms of survival are, however, limited. The aim of this study was examine the influence of rupture on patients with HCC, with particular respect to long-term survival.

Patients and methods

From 1986 to 1998, 607 consecutive patients with HCC underwent surgical treatment at the Department of Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan. Sixty-two patients, including 12 with ruptured HCC and 50 with incomplete follow-up records, were excluded from the study. The remaining 545 patients were divided into a ruptured ($n = 70$) and a non-ruptured ($n = 475$) HCC group. The 70 patients with ruptured HCC were managed according to the flow chart shown in *Fig. 1*. Twenty patients with ruptured HCC were haemodynamically unstable after conservative treatment and/or transcatheter arterial embolization (TAE). Ten of these

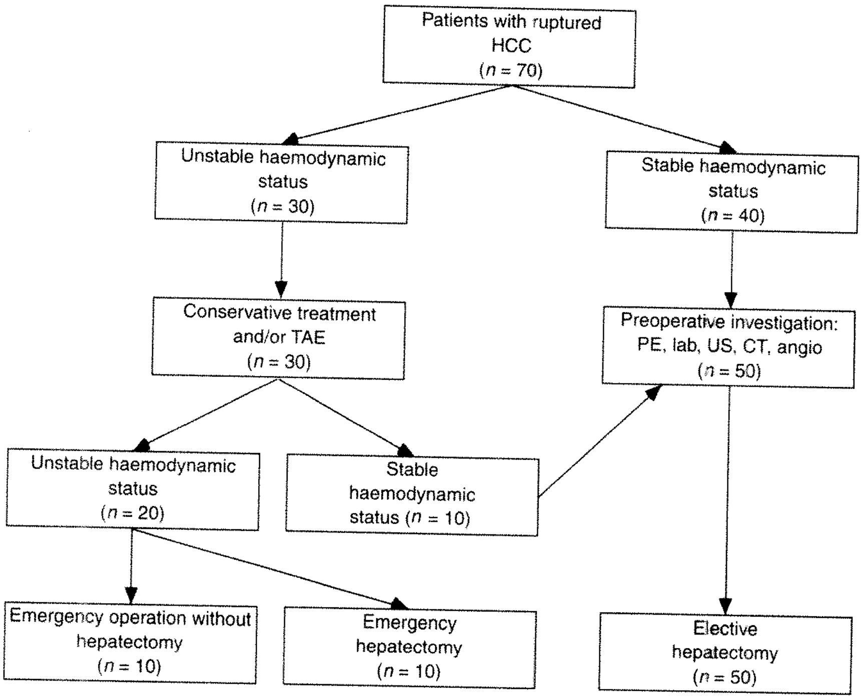

Patients with ruptured HCC (n = 70)
Unstable haemodynamic status (n = 30)
Stable haemodynamic status (n = 40)
Conservative treatment and/or TAE (n = 30)
Preoperative investigation: PE, lab, US, CT, angio (n = 50)
Unstable haemodynamic status (n = 20)
Stable haemodynamic status (n = 10)
Emergency operation without hepatectomy (n = 10)
Emergency hepatectomy (n = 10)
Elective hepatectomy (n = 50)

Fig. 1 Flow chart depicting the management of 70 patients with ruptured hepatocellular carcinoma (HCC). TAE, transcatheter arterial embolization; PE, physical examination; lab, laboratory tests; US, ultrasonography; CT, computed tomography; angio, selective angiography

patients underwent emergency operation without hepatectomy and the other ten had an emergency hepatectomy; they were not studied further. In the remaining 50 patients haemorrhage was controlled by conservative treatments and/or TAE leading to routine preoperative assessment and elective hepatectomy.

Laboratory tests were performed on the day before operation. Differences in demographics, symptomatology, physical examination, laboratory data, presence of cirrhosis, Child–Pugh grade, operative findings, pathological features, DNA status, recurrence and long-term survival between the ruptured and non-ruptured HCC groups were compared. Clinical features were considered as present or absent, haemoglobin levels as less than 10 g/dl *versus* more than 10 g/dl, aspartate aminotransferase (ASAT) as less than 34 units/l *versus* more than 34 units/l, blood loss as less than 2 litres *versus* more than 2 litres, and tumour size as less than 3 cm *versus* greater than 3 cm.

Resections included segmentectomy, lobectomy, extended lobectomy, subsegmentectomy and wedge resection. Segmentectomy is a resection of one of the four segments (lateral, medial, anterior or posterior) of the liver as classified by Healy and Schroy[7]. Subsegmentectomy is the resection of a Couinaud segment[8]. Histopathological findings of HCC were divided into four grades according to Edmondson and Stainer's system[9]. Grades I and II were combined as low-grade HCC, and grades III and IV as high-grade HCC.

Statistical analysis

All data are presented as percentages or as mean(s.d.). Numerical data were compared by independent two-sample *t* tests. Nominal data were compared with the Pearson χ^2 test, or with multiple forward stepwise logistic regression when appropriate. Survival was calculated and plots were constructed according to the Kaplan–Meier method, and compared with the log rank test. All statistical analyses were performed using the Statistical Package for the Social Sciences computer software package (SPSS®, Chicago, Illinois, USA). $P < 0{\cdot}05$ was considered statistically significant.

Results

There were 48 men and 12 women with a mean(s.d.) age of 50·3(15·8) (range 5–85) years in the ruptured HCC group. Similar age distributions and sex ratios were found in the ruptured and non-ruptured groups (*Table 1*). Sudden-onset abdominal pain and anaemia (haemoglobin concentration

Table 1 Demographic data of patients with ruptured and non-ruptured hepatocellular carcinoma

	Ruptured HCC	Non-ruptured HCC	*P*
Mean(s.d.) age (years)	50·3(15·8)	53·7(13·3)	0·074
Sex ratio (M : F)	48 : 12	367 : 108	0·632
Abdominal pain	56 of 60 (93·3)	369 of 475 (77·7)	0·003
Physical findings	25 of 60 (41·7)	126 of 475 (26·5)	0·014
HBsAg	33 of 54 (61·1)	314 of 444 (70·7)	0·147
Anti-HCV antibody	12 of 32 (37·5)	103 of 285 (36·1)	0·879
Dual infection	3 of 60 (5·0)	31 of 475 (6·5)	0·648
Associated cirrhosis	35 of 59 (59·3)	245 of 471 (52·0)	0·289
Child–Pugh grade A	37 of 47 (78·7)	361 of 426 (84·7)	0·284

HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus

less than 10 g/dl) were more common in the ruptured HCC group (*Table 1*). The percentage of patients who were positive for hepatitis B and/or C was similar between the two groups. There was no significant difference in rates of underlying liver cirrhosis or Child–Pugh grade between the two groups (*Table 1*).

The results of all preoperative laboratory tests are shown in *Table 2*. Only levels of ASAT differed between the two groups.

Operative, macroscopic and microscopic findings are summarized in *Table 3*. Similar percentages of low- and high-grade HCC were observed in the two groups. Patients with ruptured HCC had greater operative blood loss ($P = 0{\cdot}001$). Tumour size in the ruptured HCC group was

Table 2 Laboratory data for patients with ruptured and non-ruptured hepatocellular carcinoma

	Ruptured HCC	Non-ruptured HCC	*P*
α-Fetoprotein > 20 ng/ml*	35 of 50 (70·0)	300 of 443 (67·7)	0·743
Haemoglobin (g/dl)	12·2(2·6)	12·9(2·2)	0·026
White cell count (per μl)	12 132·8(17 737·7)	8 591·8(11 330·3)	0·143
Platelet count (10^3 per μl)	216·3(145·3)	184·7(118·2)	0·072
INR (%)	1·12(0·21)	1·09(0·14)	0·234
Albumin (g/dl)	3·63(0·51)	3·76(0·60)	0·202
Bilirubin (mg/dl)			
Direct	0·68(1·15)	0·64(1·35)	0·899
Total	1·33(1·43)	1·16(1·96)	0·516
Creatinine (mg/dl)	1·72(2·56)	1·43(2·62)	0·441
ASAT (units/l)	110·5(158·5)	76·5(120·4)	0·048
ALAT (units/l)	58·3(58·9)	65·0(118·2)	0·699
ALP (units/l)	98·5(49·8)	125·3(330·0)	0·559
ICG 15 (%)	12·6(11·2)	15·3(15·8)	0·527

Values are mean(s.d.); *number of patients with percentage in parentheses. INR, international normalized ratio; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ICG 15, indocyanine green retention rate at 15 min

Table 3 Operative, macroscopic and microscopic findings for patients with ruptured and non-ruptured hepatocellular carcinoma

	Ruptured HCC	Non-ruptured HCC	*P*
Major hepatectomy	26 of 60 (43·3)	252 of 475 (53·1)	
Mean(s.d.) blood loss (ml)	2487(2089)	1497(1750)	0·001
Mean(s.d.) blood transfusion (ml)	1830(1658)	1522(3127)	0·455
Mean(s.d.) tumour size (cm)	7(5)	6(4)	0·083
Tumour size >5 cm	32 of 58 (55·2)	209 of 460 (45·4)	0·161
Grading (Edmondson and Stainer)			
Low grade (I + II)	34 of 44 (77·3)	244 of 329 (74·2)	
High grade (III + IV)	10 of 44 (22·7)	85 of 329 (25·8)	0·657
Capsule formation	27 of 44 (61·4)	248 of 395 (62·8)	0·853
Capsule invasion	9 of 37 (24·3)	95 of 357 (26·6)	0·764
Macroscopic vascular invasion	23 of 56 (41·1)	151 of 453 (33·3)	0·249
Satellite lesions	18 of 56 (32·1)	133 of 447 (29·8)	0·713
Resection margin ≤ 1 cm	27 of 46 (58·7)	245 of 399 (61·4)	0·721
Recurrence	38 of 54 (70·4)	270 of 432 (62·5)	0·258
DNA diploidy	10 of 25 (40·0)	74 of 224 (33·0)	0·485

Values in parentheses are percentages unless otherwise indicated

Table 4 Multiple forward stepwise logistic regression analysis of clinicopathological features

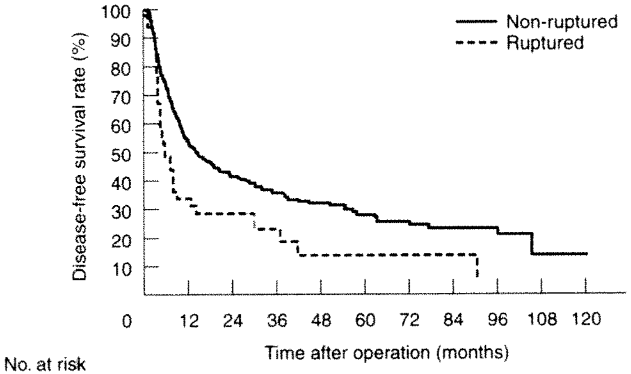
	Coefficient	s.e.	Wald statistic	Odds ratio	*P*
Sudden-onset abdominal pain	− 1·096	0·641	2·921	0·334 (0·095, 1·175)	0·047
Physical signs	− 0·437	0·337	1·348	0·646 (0·309, 1·351)	0·246
Haemoglobin < 10 g/dl	0·339	0·525	0·418	1·404 (0·502, 3·924)	0·518
ASAT > 34 units/l	− 0·034	0·437	0·006	0·966 (0·410, 2·277)	0·938
Blood loss > 2 litres	− 0·844	0·467	3·263	0·430 (0·172, 1·074)	0·071
Tumour size > 3 cm	0·214	0·473	0·205	1·239 (0·490, 3·133)	0·651

Values in parentheses are 95 per cent confidence intervals. ASAT, aspartate aminotransferase

slightly greater than that in the non-ruptured group, although this difference was not statistically significant ($P = 0{\cdot}083$). Generally, tumours in the patients in the ruptured HCC group had similar capsule formation, vascular invasion, satellite lesions, recurrence rate, DNA status and clearance margins compared with those in the non-ruptured group (*Table 3*). The overall mortality rate was 6·1 per cent (33 of 545 patients) and did not differ between the ruptured and the non-ruptured group (7·1 *versus* 5·7 per cent; $P = 0{\cdot}561$).

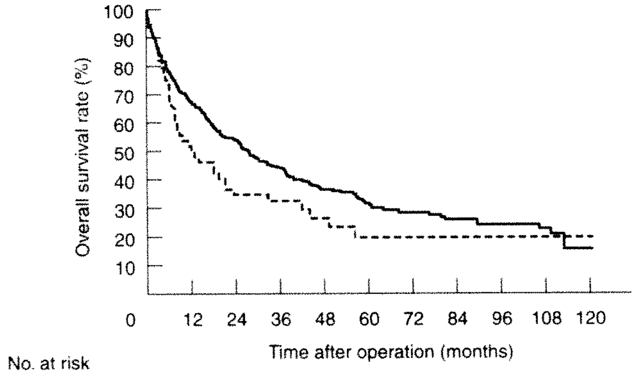
Significantly lower haemoglobin levels with raised ASAT values were observed in the ruptured HCC group ($P = 0{\cdot}003$ and $P = 0{\cdot}005$ respectively). Other biochemical data were similar between the two groups. Univariate analysis showed that sudden-onset abdominal pain, physical signs of haemodynamic unstability, lower haemoglobin level and increased ASAT levels were all associated with ruptured HCC, although multivariate logistic regression analysis showed that the presence of sudden-onset abdominal pain was the sole independent factor differentiating ruptured from non-ruptured HCC (*Table 4*).

All of the 535 patients who underwent hepatic resection were followed at regular intervals until death. The duration of follow-up ranged from 1 to 166 (median 25·6) months. Disease-free and overall actuarial survival for the two groups of patients are shown in *Fig. 2*. The 1-, 3- and 5-year actuarial survival rates were 54·2, 35·0 and 21·2 per cent respectively in the ruptured HCC group, compared with 72·1, 47·3 and 33·9 in the non-ruptured group. The 5-year disease-free survival rate was 13·4 per cent in the ruptured HCC group and 25·8 per cent in the non-ruptured group. In comparison with the ruptured HCC group, patients in the non-ruptured group had a similar overall survival ($P = 0{\cdot}074$), but significantly better disease-free survival ($P = 0{\cdot}023$).



No. at risk										
Non-ruptured	475	174	125	90	54	31	25	18	16	10	8
Ruptured	60	15	13	11	9	5	2	0	0	0	0

a Disease-free survival



No. at risk											
Non-ruptured	475	270	210	140	90	58	42	29	16	12	8
Ruptured	60	30	20	16	11	7	5	4	4	2	2

b Overall survival

Fig. 2 **a** Disease-free and **b** overall survival of 60 patients with ruptured hepatocellular carcinoma (HCC) compared with 475 patients with non-ruptured HCC. **a** $P = 0{\cdot}023$, **b** $P = 0{\cdot}074$ (log rank test)

Discussion

The incidence of HCC with spontaneous rupture shows a distinct geographical difference in reported incidence, ranging from 1 to 22 per cent[3]. In this study 60 (11·2 per cent) of the 535 patients with HCC who underwent hepatic resection had rupture.

Demographics, symptomatology, physical findings, biochemical data, hepatitis status and extent of cirrhosis were generally similar between the groups with and without rupture. Patients with ruptured HCC were different from those with no rupture in four respects: (1) they had symptoms such as a sudden attack of severe abdominal pain and signs of bleeding during physical examination; (2) a lower haemoglobin level was observed; (3) there was a higher ASAT concentration (ASAT is released by damaged cells as a consequence of increased permeability of the cell membrane or cell necrosis); and (4) greater blood loss was observed during hepatic resection. Significant sudden-onset abdominal pain was the only independent factor relating to patients with ruptured HCC, and such symptoms should alert the diagnosis of ruptured HCC, especially in an endemic area.

Treatment for ruptured HCC is aimed at control of haemorrhage and resection, when possible. The latter is strongly influenced by the extent of the tumour (e.g. bilobar disease or caval involvement). Resection is technically difficult in the cirrhotic liver, and success is dependent on the severity of cirrhosis. In a report by Lai *et al.*[10], of 56 patients with ruptured HCC, 34 (60·7 per cent) had macroscopic cirrhosis. Only seven (12·5 per cent) of these 56 patients were managed by hepatectomy. In another study from Hong Kong, Dewar *et al.*[11] reported that 36 of 37 patients with a ruptured HCC were considered to have underlying cirrhosis of the liver; 11 of these patients underwent hepatectomy. In the present series, 35 of the 59 patients with ruptured HCC had associated cirrhosis, and the resectability rate was 59·3 per cent. With recent advances in hepatic surgery, hepatic resection for ruptured HCC is feasible and provides the only hope of cure.

Previous Japanese[12] and Italian[13] studies have demonstrated that emergency hepatic resection for ruptured HCC may achieve a long-term outcome comparable with that of elective surgery in selected cases. The present report confirms comparable overall survival of patients with ruptured HCC who underwent hepatic resection compared with the non-ruptured HCC group. As observed elsewhere[12], a lower disease-free survival rate was observed in the patients with rupture who underwent hepatic resection, although the difference between groups was not statistically significant. Yamagata *et al.*[12] claimed that raised intratumour pressure with a high incidence of venous invasion was the main reason for recurrence in the ruptured HCC group. In the present study a similar percentage of vascular invasion was observed in the ruptured and non-ruptured groups. Greater blood loss with more blood transfusions might partly explain the poor disease-free survival in patients with ruptured HCC. Perioperative blood transfusion has been related to shorter disease-free survival, because of the immunosuppressive effect of transfusion[14].

The presence of sudden-onset abdominal pain was the only independently significant factor in patients with ruptured HCC, and this diagnosis must be considered in endemic areas. Hepatic resection is often feasible, and is the treatment of choice for ruptured HCC. This can result in an overall survival rate comparable to that of patients without rupture.

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Original article

Perineural invasion has a negative impact on survival of patients with gallbladder carcinoma

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Background: The clinical significance of perineural invasion of gallbladder carcinoma remains unclear. The aim of this study was to elucidate the incidence and mode of perineural invasion of gallbladder carcinoma and clarify its prognostic significance.
Methods: A clinicopathological study was conducted on 68 patients who underwent attempted curative resection for gallbladder carcinoma. According to the pathological tumour node metastasis (pTNM) classification of the Union Internacional Contra la Cancrum, there were five (7 per cent), nine (13 per cent), 20 (29 per cent) and 34 (50 per cent) patients with pT1, pT2, pT3 and pT4 disease respectively. Twenty patients (29 per cent) had pM1 disease, including involved para-aortic nodes, liver metastases and localized dissemination.
Results: The overall incidence of perineural invasion was 71 per cent (48 of 68 patients). Forty-four (96 per cent) of 46 patients with extrahepatic bile duct invasion had perineural invasion. Although several histological factors were associated with perineural invasion, multivariate analysis demonstrated that extrahepatic bile duct invasion was the only significant factor correlated with perineural invasion (odds ratio 99·0, $P < 0.001$). The perineural invasion index, defined as the ratio of the number of involved nerves to the total number of nerves examined, was significantly higher at the centre than in the proximal and distal parts of the tumour in the 46 patients with extrahepatic bile duct invasion ($P < 0.001$). The 5-year survival rate for patients with perineural invasion was significantly lower than that for patients with no invasion (7 *versus* 72 per cent; $P < 0.001$). Cox proportional hazard analysis identified perineural invasion (relative risk (RR) 5·3, $P < 0.001$) and lymph node metastasis (RR 2·5, $P = 0.008$) as significant independent prognostic factors.
Conclusion: Perineural invasion is common in advanced gallbladder carcinoma and has a significant negative impact on patient survival.

Paper accepted 29 April 2002

British Journal of Surgery 2002, **89**, 1130–1136

Introduction

Despite advances in diagnostic modalities, in most patients with gallbladder carcinoma the diagnosis is made at an advanced stage and the prognosis remains dismal[1–5]. As gallbladder cancer readily invades the liver and major vessels, extensive hepatectomy is often required to eradicate local disease. Surgical resection is the best therapeutic strategy, and the goal of therapy should be the complete removal of all cancer tissue, despite the difficulties associated with extensive surgery. Extensive hepatectomy with or without combined resection of adjacent organs is increasingly being performed for gallbladder carcinoma, and several authors have reported the utility of such a radical approach for selected patients with advanced disease[2,6–15].

The spread of tumour through the perineurium has been described in a variety of head and neck[16], prostate[17] and pancreatic[18] tumours, and many authors have emphasized nerve dissection together with tumour resection as a more radical approach[16–18]. The present authors previously reported a high incidence of perineural invasion in patients with cholangiocarcinoma, and have described its impact on survival[19,20]. Although a few authors have described perineural invasion by gallbladder cancer[21,22], its clinical significance remains unclear because no detailed studies have been conducted. A better understanding of perineural invasion is essential for determining the optimal extent of resection, including nerve dissection, to examine its impact on curability rates. The aims of this study were to elucidate the incidence and mode of perineural spread of gallbladder carcinoma and clarify its prognostic significance.

Patients and methods

Patients

From January 1989 to June 2000, 129 patients with gallbladder carcinoma were treated at the First Department of Surgery, Nagoya University Hospital. In 39 (30 per cent), resection was not undertaken because of advanced disease or the patient's poor general condition. The remaining 90 patients (70 per cent) underwent a palliative ($n = 8$) or curative ($n = 82$) resection of the tumour. A curative resection was defined as the complete removal of all macroscopic cancer tissue including both the primary tumour and metastases. Of the 82 patients who had a curative resection, 14 were excluded from the study because of a past history of another advanced cancer ($n = 2$) or lack of sufficient information ($n = 12$). The remaining 68 patients were enrolled into the study.

There were 24 men and 44 women, aged 33–82 (mean 62·8) years. According to the pathological tumour node metastasis (pTNM) classification of the Union Internacional Contra la Cancrum (UICC)[23], there were five (7 per cent), nine (13 per cent), 20 (29 per cent) and 34 (50 per cent) patients with pT1, pT2, pT3 and pT4 disease respectively. Twenty patients (29 per cent) had pM1 disease, due to positive para-aortic nodes ($n = 17$), liver metastases ($n = 2$) or peritoneal dissemination localized to the surface of the hepatoduodenal ligament ($n = 1$). The TNM stage was I in five patients (7 per cent), II in five (7 per cent), III in 16 (24 per cent), IVa in 17 (25 per cent) and IVb in 25 (37 per cent). The location of the primary tumour was the cystic duct in 16 patients, neck of the gallbladder in 18, body in 12, fundus in 8 and whole gallbladder in 14.

Operative procedures

A hepatectomy was performed in 59 (87 per cent) of the 68 patients (*Table 1*). A right hepatic lobectomy or a more extensive hepatectomy was the most common procedure. A combined resection of the extrahepatic bile duct with a bilioenteric anastomosis ($n = 56$, 82 per cent), a pancreaticoduodenectomy ($n = 18$, 26 per cent) and/or a portal vein resection ($n = 14$, 21 per cent) were also performed in selected patients. Extended clearance of lymph nodes including both the regional and para-aortic nodes[24] was carried out in all 63 patients with pT2 or more advanced disease.

Table 1 Surgical procedures performed in the 68 patients

Procedure	Total	With BD	With PD	With PV
Hepatectomy*				
S1, 4, 5, 6, 7, 8	5	5	2	1
S1, 4a, 5, 6, 7, 8	32	32	9	11
S1, 5, 6, 7, 8	4	4	3	1
S4, 5, 8	2	0	0	0
S5, 8	1	1	0	1
S4a, 5, (6)	5	4	1	0
Wedge resection	10	2	1	0
Cholecystectomy	9	8	2	0
Total	68	56 (82)	18 (26)	14 (21)

Values in parentheses are percentages. *Expressed as Couinaud's hepatic segments resected. BD, extrahepatic bile duct resection; PD, pancreaticoduodenectomy; PV, portal vein resection; S4a, inferior part of segment 4

Histological examination

The resected specimens were fixed in 10 per cent formalin. In the case of the extrahepatic bile duct, specimen cholangiography was performed before fixation. The bile duct then was longitudinally opened from the distal resection margin up to the proximal margin. The fixed, resected specimens were serially cut into 5-mm slices. Blocks made from the slices were processed through paraffin and slides were prepared in the usual manner with haematoxylin and eosin staining. Perineural invasion was defined as tumour cells found in and extending along the perineural spaces. The number of nerve fibres with or without perineural cancer invasion was counted in at least three places in each part of the tumour. The perineural invasion index (PNI) was calculated from the mean values in each part of the tumour according to the following formula[19]: PNI = number of nerve fibres with cancer invasion/total number of nerve fibres examined. In 46 patients with extrahepatic bile duct invasion of gallbladder carcinoma, the extent and mode of perineural invasion were analysed; the PNI was calculated at the proximal (resected left hepatic duct), centre (Calot's triangle) and distal (resected common bile duct) parts of the specimen. The grade of perineural invasion was based on the PNI: grade I was defined as PNI of less than 0·2 and grade II as PNI of 0·2 or more.

Statistical analysis

Results are expressed as the mean(s.d.). Statistical analyses were performed with Fisher's exact probability test and analysis of variance with the Scheffé test, where appropriate. Multivariate analysis was performed with stepwise logistic regression analysis using the Statistical Analysis System version 6·12 software (SAS Institute, Cary, North Carolina, USA). Postoperative survival was calculated using the Kaplan–Meier method, and differences in survival curves were compared with the log rank test. The Cox proportional hazard model was used for multivariate analysis of survival. $P < 0{\cdot}05$ was considered statistically significant.

Results

Association of perineural invasion with other histological factors

Of the 68 patients with gallbladder carcinoma who underwent resection, 48 (71 per cent) had perineural invasion. Pathological details of the 68 patients with and without perineural invasion are shown in *Table 2*. Histological type, lymph node metastasis, extrahepatic bile duct invasion and liver invasion showed significant associations with perineural invasion.

Logistic regression analysis involving the four significant histological factors determined by univariate analysis demonstrated that extrahepatic bile duct invasion was the only factor that correlated significantly with perineural invasion (odds ratio 99·0 (95 per cent confidence interval (c.i.) 16·6 to 589·3); $P < 0{\cdot}001$).

Perineural invasion in gallbladder cancer with extrahepatic bile duct invasion

Significant differences in the incidence of perineural invasion and PNI were observed between the centre of the tumour and the proximal or distal regions of the tumour ($P < 0{\cdot}001$) (*Table 3*). The incidence of perineural invasion and the PNI at the distal edge of the tumour were higher than those at the proximal edge of the tumour, although the differences were not statistically significant.

The mean(s.d.) PNI at the centre of the tumour was 0·32(0·21) (range 0–0·75). Proximal or distal extension of perineural invasion was observed in only one of the 15 patients with grade I perineural invasion, while it was found in 18 of the 31 patients with grade II ($P < 0{\cdot}05$). All six patients with both proximal and distal extension of perineural invasion had grade II perineural invasion (*Fig. 1*).

Table 2 Relationship between perineural invasion and other histological factors

	Perineural invasion		
	Present ($n = 48$)	Absent ($n = 20$)	P*
Histological type of adenocarcinoma			< 0·001
Papillary or well differentiated	2	9	
Moderately differentiated	35	6	
Poorly differentiated	8	3	
Other	3	2	
Lymph node metastasis			< 0·05
Negative (pN0)	22	15	
Involved regional node (pN1 or pN2)	12	2	
Involved para-aortic node (pM1)	14	3	
Lymphatic permeation			n.s.
Present	43	16	
Absent	5	4	
Vascular permeation			n.s.
Present	20	4	
Absent	28	16	
Extrahepatic bile duct invasion			< 0·001
Present	44	2	
Absent	4	18	
Liver invasion			< 0·005
Present	26	3	
Absent	22	17	

pN, pathological node; pM, pathological metastasis; n.s., not significant.*Fisher's exact test

Table 3 Perineural invasion in 46 patients with gallbladder cancer and extrahepatic bile duct invasion

Location	Incidence of perineural invasion*	PNI†
Proximal (resected left hepatic duct)	9 of 46 (20)	0·10(0·26)
Centre (Calot's triangle)	44 of 46 (96)‡	0·32(0·21)‡
Distal (resected common bile duct)	16 of 46 (35)	0·15(0·26)

*Values in parentheses are percentages; †values are mean(s.d.). PNI, perineural invasion index. ‡$P < 0{\cdot}001$ *versus* proximal or distal (analysis of variance with Scheffé test)

Survival

Of the 68 study patients, seven died from liver failure or multiple organ failure after operation, giving an overall hospital mortality rate of 10 per cent. All of these seven patients had had a major hepatectomy, and had extrahepatic bile duct invasion with perineural invasion.

Survival (excluding the seven hospital deaths) was closely associated with perineural invasion. The 5-year survival rate of patients with perineural invasion was significantly lower

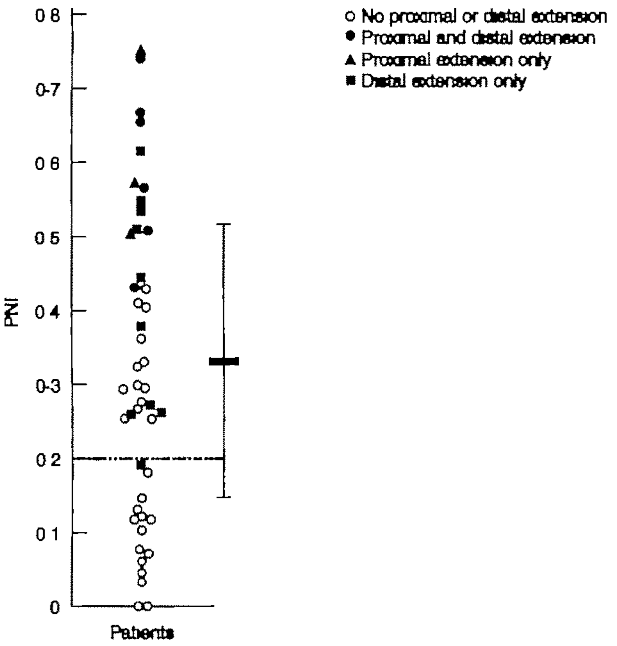

Fig. 1 Scatterplot of the perineural invasion index (PNI) at the centre of the tumour in patients with gallbladder carcinoma involving the extrahepatic bile duct. The horizontal bar indicates mean PNI with standard deviation

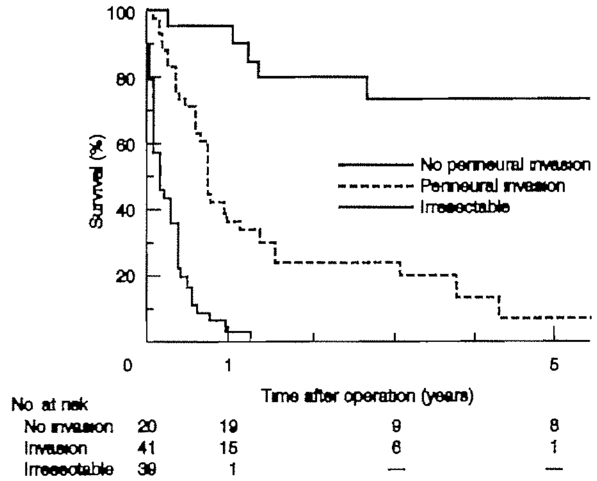

Fig. 2 Survival according to perineural invasion in patients with gallbladder carcinoma who underwent curative resection (hospital deaths excluded) $P < 0\cdot001$ (perineural invasion *versus* no invasion or irresectable, log rank test)

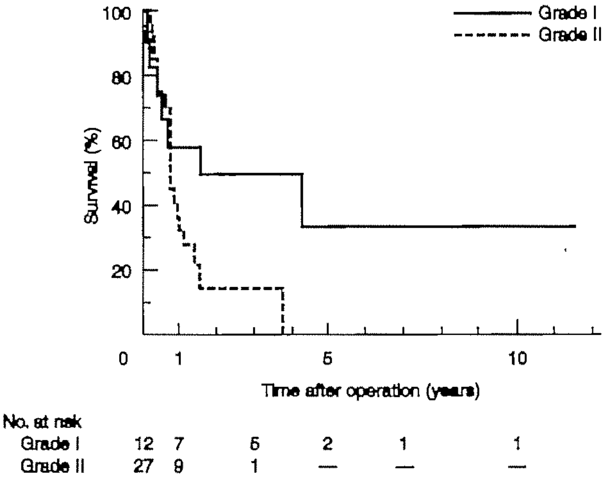

Fig. 3 Survival of patients with extrahepatic bile duct invasion (seven hospital deaths excluded). Grade I, perineural invasion index (PNI) of less than 0·2; grade II, PNI of 0·2 or more. $P = 0\cdot065$ (grade I *versus* grade II, log rank test)

than that of patients without invasion (7 *versus* 72 per cent; $P < 0\cdot001$), but significantly higher than that of patients with irresectable tumours ($P < 0\cdot001$) (*Fig. 2*).

The outcome of patients with extrahepatic bile duct invasion (excluding hospital deaths) was analysed according to the grade of perineural invasion (*Fig. 3*). Although the difference in survival rates between patients with grade I ($n = 12$) and grade II ($n = 27$) invasion was marginal ($P = 0\cdot065$), the 5-year survival rate of the former was better than that of the latter (33 *versus* 0 per cent; median survival 24 *versus* 10 months). Several types of recurrence, including local, haematogenous, nodal or peritoneal, occurred after operation. Local recurrence was observed in six of the 27 patients with grade II invasion and in no patient with grade I invasion (P not significant). The incidence of the other types of recurrence was similar between the two groups: haematogenous recurrence, six with grade I invasion *versus* 11 with grade II invasion; nodal, two *versus* three; peritoneal, two *versus* five; and unknown, none *versus* two.

Analysis of prognostic factors in patients with gallbladder carcinoma

Of the 61 patients with gallbladder cancer who survived operation, 11 independent clinicopathological variables were analysed as possible prognostic factors. On univariate analysis, histological type, lymph node metastasis (pN), perineural invasion, extrahepatic bile duct invasion, depth of tumour penetration (pT) and pTNM classification were statistically significant factors (*Table 4*). Multivariate analysis by the Cox proportional hazard model was performed using the above six significant variables. On multivariate analysis, perineural invasion and lymph node metastasis were identified as significant independent prognostic factors in patients with gallbladder carcinoma (*Table 5*).

Table 4 Univariate analysis of prognostic factors for patient survival

Modality	*n*	Overall survival rate (%)		*P*†
		3 years	5 years	
Age				
< 63 years	27	49	32	
⩾ 63 years	34	34	34	0·45
Sex				
Male	18	35	23	
Female	43	44	35	0·48
Histological type of adenocarcinoma				
Papillary or well differentiated	10	88	88	
Moderately or poorly differentiated, other	51	32	21	0·002
Lymph node metastasis				
Absent	34	60	53	
Present	27	16	5	< 0·001
Perineural invasion				
Absent	20	72	72	
Present	41	24	7	< 0·001
Lymphatic permeation				
Absent	9	67	67	
Present	52	37	27	0·19
Vascular permeation				
Absent	41	48	33	
Present	20	25	25	0·065
Extrahepatic bile duct invasion				
Absent	22	62	55	
Present	39	28	14	0·004
Liver invasion				
Absent	37	50	34	
Present	24	27	27	0·65
Depth of tumour penetration*				
T1, T2	14	75	75	
T3, T4	47	30	16	< 0·001
pTNM classification				
I, II, III	24	63	54	
IVa, IVb	37	28	18	0·004

*According to the tumour node metastasis (TNM) classification of the Union Internacional Contra la Cancrum (UICC). †log rank test

Table 5 Multivariate Cox regression analysis of prognostic factors

	Relative risk	*P*
Perineural invasion (present)	5·3 (1·20, 14·2)	< 0·001
Lymph node metastasis (present)	2·5 (1·3, 5·0)	0·008

Values in parentheses are 95 per cent confidence intervals

Discussion

The perineural space was previously thought to connect with the lymphatic system; therefore, perineural invasion was considered to reflect lymphatic invasion[25,26]. However, later studies using light and electron microscopy reported that there are no connections between the perineurium and the lymphatic system[17,27]. More recently, Maxwell *et al.*[28] studied the perineural invasion of extrahepatic bile duct carcinoma by means of a three-dimensional reconstruction, and found continuity between the isolated perineural invasion observed by conventional light microscopy and larger tumour masses, via a complex branching of the perineural network. The present study found no association between perineural invasion with either lymphatic or vascular invasion. In addition, the incidence and extent of perineural invasion were greater at the centre of the tumour than at the proximal or distal margins. These findings suggest that perineural invasion does not develop via the lymphatic or vascular network but is a continuous extension from the primary tumour, consistent with previous studies.

It is well recognized that pancreatobiliary cancer readily invades into the perineural space, the reported incidence of perineural invasion being 72–90 per cent in pancreatic cancer[18,22,29], 60–81 per cent in bile duct cancer[19,22] and 44–72 per cent in gallbladder carcinoma[21,30]. The overall incidence of perineural invasion in the present series was consistent with previous reports. An important finding arising from this study was a close association between perineural invasion and extrahepatic bile duct invasion. There are rich autonomic nerve networks in the hepatoduodenal ligament, especially around the hepatic artery and portal vein. Therefore, once gallbladder cancer invades the extrahepatic bile duct through Calot's triangle, the tumour is likely to encroach on nerve tissue and extend along the perineural space.

The authors have previously reported that perineural spread of hilar cholangiocarcinoma was significantly more common in the distal portion of the bile duct than in the proximal portion[19]. This may be due to the fact that the intrahepatic perineural space is not as wide as the extrahepatic perineural space. Therefore, a tumour might spread through the wider pathway more easily than through the narrower pathway[19,27,31]. The present study also confirmed this trend: the incidence and extent of perineural invasion was greater at the distal than at the proximal margin of the tumour, although the difference was not statistically significant. The authors recommend that the resected stump of the distal bile duct be examined during operation by frozen section in cases where gallbladder cancer involves the extrahepatic bile duct, in order to rule out unexpected distal extension of perineural invasion.

Lymph node metastasis in patients with gallbladder carcinoma is well known to be a strong indicator of poor prognosis[2,10,13,24]; but the survival impact of perineural invasion remains poorly understood. Only Chijiiwa *et al.*[21] have described the importance of perineural invasion on the survival of patients with advanced gallbladder cancer. Using multiple regression analysis these authors demonstrated that perineural invasion was a significant prognostic factor. Recently, Fong *et al.*[13] reported several prognostic factors in a large series of patients with resected advanced gallbladder carcinoma, but did not mention perineural invasion. A lack of interest in perineural invasion may result from the fact that it seems to occur exclusively in advanced cases with extrahepatic bile duct invasion. In most Western and Eastern centres, many patients with such locally advanced tumours are not candidates for surgical resection, and consequently not subjects for detailed histological examination. Many authors have pointed out a significant correlation between perineural invasion and prognosis in patients with head and neck tumours[16,32], pancreatic cancer[22,29] and bile duct cancer[19,20]. The present results also indicate that perineural invasion had a significant impact on the survival of patients with gallbladder cancer.

Greater controversy exists regarding the surgical treatment of locally advanced gallbladder carcinoma. Recommendations have ranged from simple cholecystectomy to an aggressive resection consisting of combined major hepatectomy and pancreaticoduodenectomy[6,7,15]. Studies in the past decade have provided some support for an aggressive approach by confirming the possibility of long-term survival after radical resection[6–15]. The present results do not necessarily support extensive autonomic nerve dissection in the hepatoduodenal ligament but the fact that long-term survival is possible in some selected patients with perineural invasion encourages the authors to perform extensive dissection.

In conclusion, perineural invasion is common in patients with advanced gallbladder cancer and has a significant negative impact on survival. Further studies should be undertaken to clarify whether extensive nerve dissection provides a survival benefit.

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Original article

Acute colonic diverticulitis in patients under 50 years of age

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Background: There is ongoing controversy concerning the virulence and management of diverticulitis in young patients. This study reports on the management of acute diverticulitis with reference to the virulence and outcome of the disease with respect to age.
Methods: Between January 1994 and June 1999, 327 patients were treated for acute left colonic diverticulitis. Patients were divided in two groups: those aged 50 years or less (group 1, 72 patients) and those older than 50 years (group 2, 255 patients). The diagnosis was confirmed histologically or radiologically in all patients.
Results: There were differences in gender distribution related to age ($P < 0.001$). During the first hospital stay, 226 patients (69·1 per cent) had successful conservative treatment, 78 (23·9 per cent) needed emergency surgery and 23 (7·0 per cent) had a semielective operation ($P = 0.47$). The recurrence rate was 25·5 per cent in group 1 and 22·3 per cent in group 2 ($P = 0.93$). The type of surgical procedure and grade of peritonitis in emergency patients were similar in the two groups. Overall the mortality rate in patients who underwent an operation was 16·3 per cent. The mortality rate was zero in group 1 and 2·2 per cent in group 2 after elective or semielective operation ($P = 1.0$), and zero in group 1 and 34·9 per cent in group 2 after emergency operation ($P < 0.001$).
Conclusion: Diverticulitis in young patients does not have a particularly aggressive course and the risk of recurrence is similar to that of older patients.

Paper accepted 9 May 2002

British Journal of Surgery 2002, 89, 1137–1141

Introduction

Colonic diverticulosis is common in the elderly with an incidence reaching 50 per cent in the ninth decade[1]. The majority of patients are asymptomatic and operation is rarely required[2]. However, acute complications of diverticular disease are relatively common and diverticulitis is the most frequent reason for hospital admission[3]. Although there is agreement about the surgical treatment of complications of diverticular disease, such as fistula, stenosis and massive haemorrhage, there remains controversy about the management of colonic diverticulitis in young patients. Some authors suggest that elective resection should be considered if an acute infective episode is successfully managed conservatively because of the recurrent nature of diverticulitis and the risk of subsequent serious complications[4,5]. However, others report that diverticulitis in young patients does not have a particularly aggressive nature[6,7]. This study reports on the management of patients admitted with acute diverticulitis and evaluates the virulence and outcome of the disease with respect to age.

Patients and methods

All patients admitted to hospital and treated for acute left colonic diverticulitis between January 1994 and June 1999 were included in the study. Patients were divided in two groups: those aged 50 years or less (group 1) and those older than 50 years (group 2).

The diagnosis was based on clinical examination, blood tests and radiological evaluation. If on admission patients had diffuse peritonitis or an acute abdomen of uncertain cause, abdominal ultrasonography and/or abdominal computed tomography were performed. If diffuse intra-abdominal fluid was observed, emergency operation was indicated. Since January 1998, abdominal computed tomography has been performed in all patients with clinical signs of diverticulitis. Radiological findings that confirmed the diagnosis at computed tomography were thickening of pericolic fat in mild diverticulitis, and the presence of an abscess, extraluminal air or diffuse intra-abdominal fluid in severe diverticulitis.

Conservative treatment consisted of bowel rest and at least 7 days of intravenous antibiotics. In all patients treated conservatively, barium enema, colonoscopy or both were subsequently used to corroborate the clinical diagnosis of diverticulosis after the acute episode had resolved.

Emergency operative treatment was undertaken if patients had diffuse peritonitis, septic shock, pneumoperitoneum, or if the clinical course did not improve after 48–72 h of conservative management. In surgical patients the diagnosis was confirmed at operation or by histological examination.

Following the authors' strategy for the management of left colonic emergencies[8], four types of surgical procedure were used. The first-choice operation was colonic resection and primary anastomosis with intraoperative colonic lavage (RPA). As previously noted[9], RPA was not performed in patients with faecal peritonitis, preoperative organ failure, immunocompromised status, those classified as American Society of Anesthesiologists (ASA) grade IV and patients with proximal colonic disease. Alternative interventions were Hartmann's procedure in high-risk patients, subtotal colectomy if there was associated involvement of the proximal colon and colostomy when the patient's general condition or local disease precluded resection.

Patients were operated on semielectively during the first admission because of failure to improve. Open or laparoscopic left colectomy with primary anastomosis was used in both semielective and elective operations. Elective operation was performed according to the guidelines of the American Society of Colon and Rectal Surgeons[10], which propose that all patients should be operated on after a second attack of uncomplicated diverticulitis to reduce the risk of subsequent recurrence and complications.

Patients were followed up until June 2001 (minimum 24 months, maximum 90 months). Recurrence of diverticulitis was diagnosed when the patient presented with similar symptoms and clinical findings, confirmed by radiological investigations. If an emergency operation was not required, treatment was again conservative and interval colectomy was planned.

Qualitative data were compared using the χ^2 test and two-tailed Fisher's exact test. Student's t test or Mann–Whitney U test was used to compare quantitative data. $P < 0{\cdot}05$ was considered significant.

Results

Some 327 patients, 156 men (47·7 per cent) and 171 women (52·3 per cent) were admitted during the study period. None had been admitted previously for diverticulitis. Although 62 (19·0 per cent) had suffered previous abdominal symptoms, 265 (81·0 per cent) had symptoms of diverticular disease for the first time during the first admission.

Table 1 Treatment during the first hospital admission

	Group 1 (≤ 50 years)	Group 2 (> 50 years)	Total
Conservative treatment	47 (65·3)	179 (70·2)	226 (69·1)
Emergency operation	19 (26·4)	59 (23·1)	78 (23·9)
Semielective operation	6 (8·3)	17 (6·7)	23 (7·0)
Total	72 (22·0)	255 (78·0)	327

Values in parentheses are percentages. There were no significant differences in type of treatment between the two groups ($P = 0{\cdot}47$, χ^2 and two-tailed Fisher's exact tests)

Group 1 included 72 patients (22·0 per cent), 51 men (70·8 per cent) and 21 women (29·2 per cent). Group 2 comprised 255 patients (78·0 per cent), 105 men (41·2 per cent) and 150 women (58·8 per cent). The differences in gender distribution with respect to age were significant ($P < 0{\cdot}001$).

Types of treatment (medical or surgical) during the first hospital stay are reported in *Table 1*. There were no significant differences between the two groups ($P = 0{\cdot}47$).

Fifty-two of the 327 patients (15·9 per cent) developed recurrent diverticular disease. None of those who were operated on as an emergency during first admission had a recurrence during the follow-up period. The median interval between the primary episode and the recurrent disease was 7·4 months in group 1 and 8·4 months in group 2 ($P = 0{\cdot}93$). If patients who underwent primary operative treatment are excluded, the overall recurrence rate was 23·0 per cent, 25·5 per cent (12 of 47) in group 1 and 22·3 per cent (40 of 179) in group 2 ($P = 0{\cdot}93$).

Of patients admitted because of acute recurrent diverticulitis, one of 12 in group 1 and three of 40 in group 2 were operated on as an emergency, while seven in group 1 and 26 in group 2 had an elective operation ($P = 0{\cdot}88$). Four patients in group 1 and seven in group 2 refused surgery. Three of these seven patients were operated on after a third attack (one as an emergency and two electively). Operation was discouraged after the second episode of diverticulitis in four patients in group 2, because of advanced age and high risk.

Number and types of surgical procedures related to age are reported in *Table 2*. There were no significant differences between the two groups with respect to emergency, elective or semielective surgery.

According to the Hinchey classification[11], the grade of peritonitis of patients operated on as an emergency was: stage 1, no patients in group 1 and four (6·3 per cent) in

Table 2 Surgical procedures for first and recurrent episodes related to age

	Group 1 (≤ 50 years)	Group 2 (> 50 years)	Total
Elective and semielective left colectomy and primary anastomosis	13	45	58
Laparoscopic	3	5	8
Laparotomy	10	40	50
Emergency operation	20	63	83
RPA	11	29	40
Hartmann's operation	7	29	36
Subtotal colectomy	2	4	6
Colostomy	0	1	1
Total	33	108	141

RPA, resection and primary anastomosis with intraoperative colonic lavage. There were no significant differences in type of elective/semielective ($P = 0.48$) or emergency ($P = 0.54$) operation between the two groups (χ^2 and two-tailed Fisher's exact tests)

group 2; stage 2, six (30·0 per cent) in group 1 and 18 (28·6 per cent) in group 2; stage 3, 11 (55·0 per cent) in group 1 and 32 (50·8 per cent) in group 2; stage 4, three (15·0 per cent) in group 1 and nine (14·3 per cent) in group 2. There were no statistically significant differences between the two groups ($P = 0.67$).

Among the 327 patients admitted with acute diverticular disease there were 23 deaths (7·0 per cent) within 30 days. The mortality rate in the surgical group was 16·3 per cent (23 of 141). The mortality rate after elective and semi-elective operations was 1·7 per cent (one of 58), zero in group 1 and 2·2 per cent in group 2 ($P = 1.0$); the patient died after a myocardial infarction. Among patients operated on as an emergency, 26·5 per cent died (22 of 83), 17 patients treated by Hartmann's procedure, three by subtotal colectomy and two patients by RPA. The mortality rate was zero in group 1 and 34·9 per cent in group 2 (22 of 63) ($P < 0.001$). Sixteen patients (19·3 per cent) died as a consequence of persistent septic shock, four after a myocardial infarction, one as a result of anastomotic dehiscence and the other after massive upper gastrointestinal haemorrhage.

The mortality rate among patients treated conservatively was zero in group 1 and 0·7 per cent (one of 147) in group 2. One patient died from a myocardial infarction 1 year after the acute episode of diverticulitis.

The hospital stay after elective surgery was 13·7 days in group 1 and 15·1 days in group 2 ($P = 0.32$); after emergency surgery, it was 16·2 days in group 1 and 16·3 days in group 2 ($P = 0.43$).

Discussion

Only a small proportion (5–10 per cent) of patients who develop diverticulitis are younger than 50 years[12,13]. In the present study, the proportion of young patients was higher than that in other studies; 22·0 per cent of patients were admitted for the first time aged less than 50 years. This could be explained by the increase in prevalence of diverticular disease, particularly in western countries[10].

There continues to be controversy concerning the virulence of diverticulitis in young patients and the most appropriate management of those whose acute diverticulitis resolves with medical treatment. Diverticulitis in younger patients has been reported to have a more aggressive course or to require emergency surgery more frequently than that in the general population[4,5,12,14,15]. In a prospective study of 226 patients with left colonic diverticulitis, Ambrosetti *et al.*[16] observed that patients younger than 50 years were more prone to recurrences after conservative treatment, whereas older patients required operations significantly more often during their first hospital admission. Ouriel and Schwartz[17] followed 92 patients under the age of 40 years who were admitted with diverticulitis. They observed that 55·2 per cent of patients, initially managed medically, required readmission. Furthermore 43·2 per cent underwent urgent surgery for complications of the disease. Given the high rates of recurrence and complication during the follow-up period they concluded that 'elective resection after a cooling period appeared to be the safest alternative'.

In the present experience, when patients who underwent primary operative treatment were excluded, the recurrence rate was similar in the two groups. Furthermore, the proportion of patients who needed emergency surgery during the first episode was similar.

In contrast to other authors[4], who observed that readmission of patients younger than 50 years was associated with the need for surgical intervention in 55·0 per cent of the cohort, in the present study only one of 12 patients under 50 years and three of 40 patients older than 50 years needed emergency surgery during the second episode of acute diverticulitis. Further support for a more conservative approach can be found in a study by Simonowitz and Paloyan[18] who identified 33 hospitalized patients under the age of 40 years, nine of whom underwent surgery during the initial admission. With a mean follow-up of 52 months, none of the remaining 24 patients required surgery.

The optimal surgical approach to complicated diverticular disease remains controversial. Tudor *et al.*[19] recommended early laparotomy and Hartmann's resection if percutaneous drainage is unsuccessful because sepsis is poorly tolerated by the elderly. Others have suggested that a two-stage procedure is the safest option in the presence of peritonitis[20] or that a one-stage procedure is indicated when infection is localized[21,22]. A recent study[9] showed that generalized purulent peritonitis and age by themselves are not contraindications to resection, perioperative lavage and primary anastomosis when performed in selected patients and by experienced surgeons.

The overall mortality rate was higher after emergency than elective surgery. Among patients operated on as an emergency it was higher in older patients. Sixteen of 83 patients died as a consequence of persistent sepsis and the mortality rate was higher in the patients who had a Hartmann's procedure. The difference in mortality rates between surgical groups can be explained by differences in the characteristics of the patients. The authors have studied the predictive value of several factors in left colonic peritonitis and observed that ASA score and preoperative organ failure are the only significant predictors of outcome in multivariate logistic regression[23]. They only perform Hartmann's procedure in selected patients with poor general condition, ASA IV, immunocompromised status, faecal peritonitis or when preoperative organ failure is observed.

There was no specific evidence of the aggressive nature of diverticular disease in young patients in this study. The severity of peritonitis, as assessed by the Hinchey classification, was no different in younger or older patients. Furthermore, the risk of a poor outcome after a second episode, following successful conservative management of the acute attack, was similar in younger patients to that of patients older than 50 years. Diverticulitis in young patients was associated with a rate of emergency operation similar to that of older patients, without differences in the grade of peritonitis. The majority of patients did not require surgery after an initial episode that responded to medical treatment and a single attack of diverticulitis in young patients did not warrant an elective resection. The authors therefore believe that diverticular disease in young patients is no different from that affecting older patients and should be managed according to the same protocol.

The risk after a second episode of diverticulitis treated conservatively without an elective operation remains to be determined. A prospective randomized trial might resolve this issue.

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Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands

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Background: Local control and survival following surgical treatment of rectal cancer have been improved by the introduction of total mesorectal excision (TME). The aim of this study was to determine the nationwide impact of the introduction and training of TME on recurrence and survival in rectal cancer.

Methods: Short- and long-term outcomes of a recently published trial of rectal cancer surgery (TME trial) were compared with results from an older trial (cancer recurrence and blood transfusion (CRAB) trial), in which conventional surgery was performed without quality control. Only patients who were operated on with curative intent and who did not receive neoadjuvant radiotherapy were studied. Differences in clinicopathological characteristics were corrected for by multivariate analysis. To ensure valid comparisons, only events that occurred within 2 years of operation were analysed with regard to long-term outcome.

Results: In the univariate analysis, a higher clinical anastomotic leak rate was found in patients following low anterior resection in the TME trial ($P = 0{\cdot}046$), but this association was not significant in the multivariate analysis. The local recurrence rate decreased from 16 per cent in the CRAB trial to 9 per cent in the TME trial, and type of operation (conventional (CRAB trial) *versus* TME (TME trial)) was an independent predictor of local recurrence ($P = 0{\cdot}002$). Type of operation was also an independent predictor of overall survival ($P = 0{\cdot}019$); there was a higher survival rate in the TME trial.

Conclusion: The introduction and training of TME has led to improved long-term outcome of patients with rectal cancer in the Netherlands.

Paper accepted 9 May 2002

British Journal of Surgery 2002, **89**, 1142–1149

Introduction

In the Netherlands, 8000 new patients with colorectal cancer were registered in 1995, of whom about 25 per cent had rectal carcinoma[1]. A major problem in the treatment of rectal carcinoma is local recurrence. In the literature, the reported incidence of local recurrence after curative resection varies widely; the highest incidence has been reported in studies of so-called 'conventional' resection that entails blunt non-standardized dissection[2–4]. In recent years local control and survival have improved with the introduction of total mesorectal excision (TME)-based surgery[2,5–8]. TME is accomplished by precise sharp dissection under direct vision within the true pelvis around the integral mesentery enveloping the entire mid-rectum, with preservation of the hypogastric plexus. Using the TME technique, a reduction in the rate of abdominoperineal resection has also been achieved[7].

The Dutch ColoRectal Cancer Group (DCRCG) was established to conduct trials in order to improve the outcome of colorectal cancer treatment in the Netherlands. In the cancer recurrence and blood transfusion (CRAB) trial, patients with colorectal cancer were randomized to receive leucocyte-depleted or buffy coat-depleted blood transfusion, if required, between 1987 and 1990[9]. In this trial, conventional surgery was performed without quality control. The randomized TME trial investigated the role of preoperative short-term radiotherapy in combination with standardized TME surgery in patients with rectal cancer, and was conducted between 1996 and 1999[10]. In the trial, TME was introduced on a nationwide basis and performed according to strict and controllable quality demands.

The aim of this paper was to assess the effect of the introduction and training of TME on outcome of rectal cancer in the Netherlands. Outcomes of the TME trial were compared with results from the CRAB trial.

Patients and methods

Cancer recurrence and blood transfusion trial

Between June 1987 and December 1990, patients with colorectal cancer in the CRAB trial were randomized to transfusion of leucocyte-depleted or buffy coat-depleted blood and received blood transfusion upon indication. Eligibility criteria were histologically or radiologically proven primary adenocarcinoma of the colorectum without clinical evidence of distant metastases. In total, 1108 patients with colorectal cancer were randomized from 16 Dutch hospitals. Colorectal cancer recurrence rates were not influenced by blood transfusion; however, blood transfusion was associated with more postoperative infections and affected overall survival by an association with non-cancer death[9].

Rectal cancer affected 311 patients. A rectal tumour was defined as a tumour with an inferior margin within 15 cm of the anal verge (as measured before operation during withdrawal of a flexible endoscope). Patients with rectal cancer in the CRAB trial had conventional, non-standardized surgery without quality control. The procedure was considered to be curative when a macroscopically local radical resection was obtained in the absence of intraoperative metastases. Tumour pathology was classified according to the tumour node metastasis (TNM) system[11].

Of the 311 patients with rectal cancer, 281 were eligible and operated on for cure. Nine of these patients received preoperative radiotherapy of 30–50 Gy in six hospitals. Indications for postoperative radiotherapy of 45–60 Gy were tumour spillage during operation, Dukes' Astler–Coller B2 and C tumours, or positive resection margins. Thus 105 of 281 eligible patients who were not irradiated before operation received postoperative radiotherapy. Median follow-up of surviving patients in the CRAB trial was 78 (range 34–114) months.

Total mesorectal excision trial

A phase III trial 'Total mesorectal excision with or without short-term preoperative radiotherapy in the treatment of primary rectal cancer' was conducted between January 1996 and December 1999. This trial evaluated the effect of preoperative radiotherapy of 25 Gy over 5 days in combination with standardized TME surgery and pathological assessment[10]. Patients were randomized by Dutch, Swedish, other European and Canadian participants; however, this paper concerns only Dutch patients. Clinically operable patients with a histologically proven primary adenocarcinoma of the rectum without evidence of distant metastases were eligible. In total, 1530 patients were randomized from 84 Dutch hospitals. The trial was shown to be feasible[12] and preoperative radiotherapy appeared to reduce the risk of local recurrence in patients who underwent TME[10].

The height of the tumour was defined before operation by its inferior margin as measured during withdrawal of a flexible scope. An extensive structure of workshops, symposia, instruction videos and a monitoring committee of specially trained instructor surgeons helped to ensure that TME was performed according to strict quality criteria. TME was taught to surgeons who generally deal with rectal cancer (one to three surgeons per hospital surgical unit). In each participating hospital the first five TMEs were supervised by an instructor surgeon. A curative resection was defined as a macroscopically radical local tumour resection without intraoperative detection of metastases. Pathological examination was performed according to the protocol of Quirke *et al.*[13] with special attention to circumferential margin involvement. Carcinomas were classified according to the TNM system[11]. Half of the patients received preoperative radiotherapy of 25 Gy in 5 days. In patients randomized to TME alone, postoperative irradiation of 50–60 Gy was mandatory in cases of tumour spillage during surgery or tumour infiltration within 1 mm of the circumferential resection margin. Median follow-up of surviving patients in the TME trial was 28 (range 3–56) months.

Trial comparison

Patients who were eligible and who had undergone abdominal surgery for cure were compared. To ensure homogeneity between the trials, patients who had preoperative radiotherapy were excluded from the analysis in order to analyse the influence of the surgical technique alone.

Of the 311 patients with rectal cancer in the CRAB trial, 281 were eligible and operated on for cure. Of these patients, nine who received preoperative radiotherapy and three who underwent polypectomy for the primary tumour were excluded. In the TME trial, 1352 of 1530 patients were eligible and operated on for cure. Of these patients, 691 patients were excluded because they received preoperative radiotherapy. Thus the number of eligible patients, curatively operated on and who had not undergone preoperative irradiation, was 269 in the CRAB trial and 661 in the TME trial.

The short-term outcomes analysed in both trials were operating time, blood loss during operation, hospital stay, anastomotic leakage, wound infection and 30-day mortality. Anastomotic leakage was defined on clinical grounds. Wound infection was defined as either abdominal or perineal wound infection. Deaths within 30 days after surgery were those that occurred either before or after hospital discharge.

Long-term outcomes analysed included local and distant recurrence and overall survival. Local recurrence was defined as the presence of any histologically or radiologically proven anastomotic, pelvic or perineal tumour. Distant recurrence involved evidence of tumour in any area other than the pelvis. Overall survival concerned deaths from any cause, with or without tumour. To ensure valid comparisons, only events that occurred within 2 years of operation in both trials were analysed.

Statistical analysis

χ^2 tests were used to compare proportions. Mann–Whitney tests were used to compare quantitative and ordinal variables. Multivariate analyses of determinants of short-term outcomes, including type of operation (conventional (CRAB trial) *versus* TME (TME trial)), were done with linear and logistic regression models. For long-term outcomes univariate analyses were carried out by the Kaplan–Meier method and log-rank test. Multivariate analyses were performed with the Cox proportional hazards model. Interaction terms of factors with type of operation were included in the regression models to correct for differences in the effect of factors between the trials. For example, the effect of postoperative radiotherapy in each trial might have been different because the indications for radiotherapy were different between the trials.

Results

Clinicopathological characteristics (*Table 1*)

Table 1 Clinicopathological characteristics of eligible, curatively operated, preoperatively non-irradiated patients

	CRAB trial (n = 269)	TME trial (n = 661)	P*
Gender			0·002
Male	140 (52)	415 (63)	
Female	129 (48)	246 (37)	
Median (range) age (years)	67 (36–89)	66 (23–92)	0·03
Tumour location (cm)			0·31
0–5	69 (33)	215 (33)	
5·1 –10	93 (44)	260 (40)	
10·1–15	48 (23)	183 (28)	
Unknown	59	3	
Type of resection			0·70
Low anterior resection	173 (64)	432 (65)	
Abdominoperineal resection	89 (33)	206 (31)	
Hartmann	7 (3)	23 (3)	
TNM stage			0·09
I	92 (34)	203 (31)	
II	87 (32)	186 (28)	
III	90 (33)	272 (41)	
Adjuvant radiotherapy			< 0·001
No	168 (62)	587 (89)	
Yes	101 (38)	74 (11)	
Adjuvant chemotherapy			< 0·001
No	269 (100)	626 (95)	
Yes	0	35 (5)	

Values in parentheses are percentages. CRAB, cancer recurrence and blood transfusion; TME, total mesorectal excision. TNM, tumour node metastasis. *χ^2 test

In the CRAB trial significantly more women (P = 0·002) and older patients (P = 0·03) were treated. More patients had postoperative radiotherapy (P < 0·001) in the CRAB trial, while postoperative chemotherapy was more often applied in the TME trial (P < 0·001). Tumour location, type of resection and TNM stage did not differ between the trial groups. The variables in this table and their interactions with type of operation were used in the multivariate regression models to compensate for differences in case-mix.

Short-term outcomes (*Table 2*)

Operating time, blood loss during operation and hospital stay did not differ significantly between the two trials, although the difference in blood loss was of borderline significance (median 900 *versus* 1000 ml; P = 0·06). Clinical anastomotic leakage was reported significantly more often in the TME trial (P = 0·046), even though there was a higher proportion of temporary stomas in patients who underwent low anterior resection in this trial (CRAB 25 per cent *versus* TME 55 per cent; P < 0·001). The rates for wound infection were 8 and 9 per cent, and the 30-day mortality rate was 4 and 2 per cent in the CRAB and TME trial respectively (P not significant). In the multivariate analysis, type of operation was not an independent predictor for anastomotic leakage when corrected for case-mix.

Table 2 Short-term outcomes

	CRAB trial (*n* = 269)	TME trial (*n* = 661)	*P*§
Operating time (min)*	180 (65–420)	180 (70–380)	0·50
Blood loss during operation (ml)*	900 (0–9445)	1000 (20–15 000)	0·06
Hospital stay (days)*‡	15 (1–120)	14 (0–169)	0·11
Clinical anastomotic leakage†¶	11 of 173 (6)	51 of 432 (12)	0·046
Wound infection (abdominal or perineal)†	21 (8)	61 (9)	0·49
Death within 30 days†	12 (4)	16 (2)	0·10

*Values are median (range); †values in parentheses are percentages. ‡Postoperative deaths were included for analysis of hospital stay. ¶In patients who had low anterior resection. CRAB, cancer recurrence and blood transfusion trial; TME, total mesorectal excision. §χ^2 test and Mann–Whitney *U* test. Type of operation was not an independent predictor for any of the short-term outcomes including leakage

Long-term outcomes (*Tables 3* and *4*)

Local recurrence ($P = 0{\cdot}002$) and overall survival ($P = 0{\cdot}002$) 2 years after operation differed significantly between the CRAB and the TME trial. No significant difference was found in the risk of distant recurrence between the trials ($P = 0{\cdot}86$) (*Table 3*). In the multivariate analysis (*Table 4*), type of operation was an independent predictor for local recurrence (hazard ratio (HR) TME 0·02 (95 per cent confidence interval (c.i.) 0·00 to 0·22); $P = 0{\cdot}002$) (*Fig. 1*) in addition to TNM stage ($P = 0{\cdot}006$). TNM stage was the only independent predictor for distant recurrence ($P < 0{\cdot}001$) (*Fig. 2*). Type of operation was also an independent predictor for overall survival (HR TME 0·21 (95 per cent c.i. 0·06 to 0·78); $P = 0{\cdot}019$) (*Fig. 3*), in addition to TNM stage and age. Interactions between factors and type of operation were corrected for, but not mentioned in *Table 4* when a significant independent predictive value was found.

To check whether there was a bias in the databases (data of the CRAB trial were more mature than those of the TME trial owing to longer follow-up), the multivariate analysis was repeated for long-term outcomes separately for events occurring in the first year compared with those in the first and second years. No major differences in size or direction of the Cox regression coefficients were found between these analyses.

Table 3 Long-term outcomes

	CRAB trial (*n* = 269)	TME trial (*n* = 661)	*P**
Local recurrence risk after 2 years (%)	16	9	0·002
Distant recurrence risk after 2 years (%)	17	17	0·86
Overall survival after 2 years (%)	77	86	0·002

CRAB, cancer recurrence and blood transfusion; TME, total mesorectal excision. *Kaplan–Meier method and log-rank test

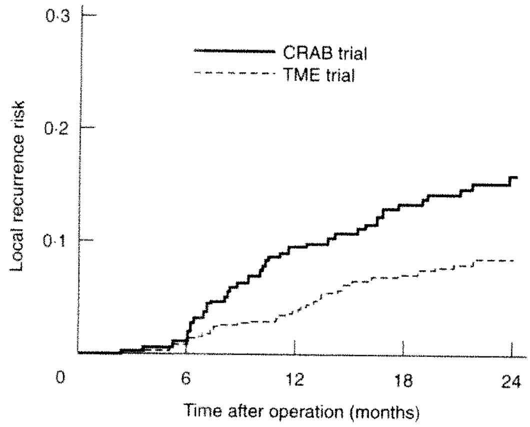
Table 4 Multivariate Cox regression model

Outcome variable	Input variable	Hazard ratio	*P*
Local recurrence risk	Type of operation		0·002
	Conventional	1·00	
	TME	0·02 (0·00, 0·22)	
	TNM stage		0·006
	I	1·00	
	II	2·37 (0·85, 6·64)	
	III	5·18 (1·86, 14·4)	
Distant recurrence risk	TNM stage		0·001
	I	1·00	
	II	2·90 (0·75, 11·2)	
	III	9·87 (2·67, 36·5)	
Overall survival	TNM stage		0·004
	I	1·00	
	II	1·80 (0·77, 4·19)	
	III	3·95 (1·70, 9·20)	
	Type of operation		0·019
	Conventional	1·00	
	TME	0·21 (0·06, 0·78)	
	Age	1·80 (1·01, 3·29)	0·05

Values in parentheses are 95 per cent confidence intervals. The baseline characteristics of *Table 1* were used as input variables, including type of operation, and long-term outcomes were used as outcome variables. Only significant input variables are listed. Age was analysed as a binary variable; cut-off point was the median (66 years). TME, total mesorectal excision; TNM, tumour node metastasis

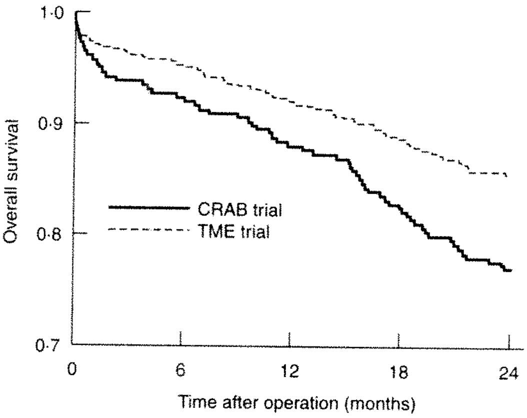
Discussion

The major problem in the treatment of rectal cancer is local recurrence. A high incidence of local recurrence is associated with conventional, non-standardized surgical procedures[3,4]. In recent years local control and survival have improved with the introduction of TME[2,5–8]. The aim of this study was to assess the effect of the introduction and training of TME on outcome of rectal cancer by analysing data from two large prospective randomized trials per-



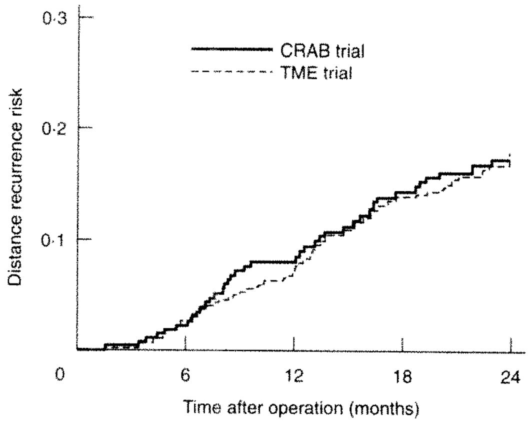
No. at risk					
CRAB trial	269	243	213	193	180
TME trial	661	614	540	428	345

Fig. 1 Kaplan–Meier plot showing influence of type of operation on local recurrence risk. CRAB, cancer recurrence and blood transfusion; TME, total mesorectal excision. Cox model: hazard ratio TME 0·02 (95 per cent confidence interval 0·00 to 0·22), $P = 0·002$



No. at risk					
CRAB trial	269	249	237	223	207
TME trial	661	626	558	449	363

Fig. 3 Kaplan–Meier plot showing influence of type of operation on overall survival. CRAB, cancer recurrence and blood transfusion; TME, total mesorectal excision. Cox model: hazard ratio TME 0·21 (95 per cent confidence interval 0·06 to 0·78), $P = 0·019$



No. at risk					
CRAB trial	269	242	213	192	179
TME trial	661	605	531	410	327

Fig. 2 Kaplan–Meier plot showing influence of type of operation on distant recurrence risk. CRAB, cancer recurrence and blood transfusion; TME, total mesorectal excision. Cox model: hazard ratio TME 0·32 (95 per cent confidence interval 0·06 to1·59), $P = 0·16$

formed in the Netherlands. In the CRAB trial[9] conventional surgery was used, whereas in the TME trial[10] TME was introduced and quality-controlled by specially trained instructor surgeons.

This paper shows that the introduction of TME has led to a substantially lower local recurrence rate when events are analysed within 2 years of operation: 16 per cent in the CRAB trial compared with 9 per cent in the TME trial. The type of operation was an independent predictor of local recurrence in the multivariate analysis. Before the start of the TME trial there were doubts about whether the excellent results of specialized surgeons[2,5,6] could be repeated in a large multicentre trial. With the low local recurrence rate in the TME trial, it is concluded that good results can also be achieved widely with thorough surgical instruction. It is remarkable that this result has been achieved in a relatively short time (4 years) with a large number of surgeons participating in the trial ($n = 213$), especially as some surgeons performed a restricted number of TME procedures. The present findings are in agreement with the report of Marting *et al.*[7]. They compared outcomes in the Stockholm I and II randomized trials, in which conventional surgery with or without preoperative radiotherapy was performed, with those of the TME project that introduced the concept of TME to surgeons in Stockholm, and found that 2-year local recurrence rates had decreased from 14–15 to 6 per cent.

In the present study, the type of operation also appeared to be an independent predictor of overall survival, with a higher survival rate in the TME trial. However, this result should be interpreted with caution since follow-up of the TME trial is shorter than that in the CRAB trial. The type of operation was not associated with distant recurrence, which is in agreement with the results of Kockerling *et al.*[14]. Both studies suggest that distant recurrence rate is independent of the quality of surgery. This may be explained by assuming that metastases were already present in the form of systemic minimal residual disease at the time of primary surgery.

In addition to better results in terms of recurrence, the introduction of TME has been reported to result in a reduction in the number of abdominoperineal resections[7]. This effect was not observed in the present comparison. In the univariate analysis, a higher clinical anastomotic leak rate was found in patients following low anterior resection in the TME trial, but this association was not significant in the multivariate analysis. Higher anastomotic leak rates with TME compared with conventional surgery have been reported previously[15,16]. An additional analysis showed that clinical anastomotic leakage was related to postoperative mortality in both trials ($P = 0\cdot024$ and $P = 0\cdot001$ respectively), but no difference in 30-day mortality rate was found. This can be explained by the large number of temporary stomas in the TME trial (55 per cent), which might have prevented a higher mortality rate from leakage[17].

An advantage of analysing data from prospective trials is that stringent follow-up, particularly when long-term outcome is an endpoint, is often present, whereas in retrospective analysis these data are often absent. Nevertheless, some biases must be ruled out concerning the analyses. The present study compared two trials performed in time periods with different numbers of patients and length of follow-up. However, inclusion and classification criteria were the same, data on outcome were collected in an equally uniform way, only events within 2 years were analysed and differences in clinicopathological characteristics were corrected for by means of multivariate analyses. Admittedly, the data from the CRAB trial are more mature than those from the TME trial. However, a minimum follow-up of 2 years is considered to be sufficient because 55–80 per cent of local recurrences present during the first 2 years with a peak incidence at 6–12 months[18,19]. In addition, no major differences in size or direction of the Cox regression coefficients were found between the multivariate analysis for events occurring in the first year compared with those in the first and second years. Another point of criticism is that the present results might not specifically address the TME issue, as other changes (for example better instruments) may have occurred at the same time as TME was introduced. Besides surgical technique, pathology data on circumferential margin involvement may also not be comparable between the trials because pathology in the TME trial focused specifically on this issue. However, staging of tumours was performed according to the same classification[11]. Finally, the question can be raised of whether this analysis represents developments in all parts of the Netherlands. This is probably the case, as patients were randomized from hospitals throughout the country in both trials.

In conclusion, this study shows that the introduction and training of TME has led to improved outcome. In the Netherlands, TME-based operations are now established as the standard of care for rectal cancer, and should form the basis for trials concerning the role of (neo)adjuvant therapy. However, training and quality control are prerequisites to obtain good results in all surgeons' hands. It is of utmost importance that, outside the setting of clinical trials, standardization of treatment is also applied and sustained. Population-based cancer registries, covering an increasing proportion of the world's population, are an invaluable source of data for these goals.

Acknowledgements

Supported by grants from the Dutch Foundation for Preventive Medicine (Praeventiefonds 28–1707, The Hague), the Macropa Foundation (Leiden), the Dutch Health Insurance Funds Council (Amstelveen), the NPBI (Emmer-Compascuum, Netherlands), the Dutch Cancer Society (CKVO 95–04) and the Dutch National Health Council (OWG 97/026). The authors thank C. W. Taat and C. A. M. Marijnen for critically reading and commenting on the manuscript.

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Evaluation of POSSUM in patients with oesophageal cancer undergoing resection

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Background: The Physiogical and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) has been used to produce a numerical estimate of expected mortality and morbidity after a variety of general surgical procedures. The aim of this study was to evaluate the ability of POSSUM to predict mortality and morbidity in patients undergoing oesophagectomy.

Methods POSSUM predictor equations for morbidity and mortality were applied retrospectively to 204 patients who had undergone oesophagectomy for cancer. Observed morbidity and mortality rates were compared with rates predicted by POSSUM using the Hosmer–Lemeshow goodness-of-fit test. Evaluation of the discriminative capability of POSSUM predictor equations was performed using receiver–operator characteristic (ROC) curve analysis.

Results: The observed and predicted mortality rates were 12·7 and 19·1 per cent respectively, and the respective morbidity rates were 53·4 and 62·3 per cent. However, the POSSUM model showed a poor fit with the data both for the observed 30-day mortality ($\chi^2 = 16{\cdot}26$, $P = 0{\cdot}002$) and morbidity ($\chi^2 = 63{\cdot}14$, $P < 0{\cdot}001$) using the Hosmer–Lemeshow test. ROC curve analysis revealed that POSSUM had poor predictive accuracy both for mortality (area under curve 0·62) and morbidity (area under curve 0·55).

Conclusion These data suggest that POSSUM does not accurately predict mortality and morbidity in patients undergoing oesophagectomy and must be modified.

Paper accepted 29 April 2002

British Journal of Surgery 2002, **89**, 1150–1155

Introduction

Morbidity and mortality rates are crude outcome measures. Risk-adjusted models, taking into account variations in case mix, reveal more about the quality of care[1–5]. Acute Physiology And Chronic Health Evaluation (APACHE) II has found wide application in intensive care patients[2] and, although it produces a numerical estimate of mortality, it ignores morbidity rates and does not take into consideration the severity of the surgical insult. The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) is a risk prediction model based on 12 characteristics of the patient and six characteristics of the operation[5]. It is superior to APACHE II for the prediction of postoperative death in patients undergoing surgery in a high-dependency unit[6]. POSSUM has been used to make comparisons between different vascular[7,8] and colorectal[9] surgical units, and to compare individual surgeons' performance within a single unit[10,11]. However, POSSUM was developed for quality assessment in general surgical units and it would not be appropriate to use this model for specific subgroups of patients unless good model performance within those subgroups could be demonstrated. This is the first study to assess the accuracy of POSSUM in predicting mortality and morbidity in patients with oesophageal cancer undergoing resection.

Patients and methods

Between January 1990 and December 1999, 213 patients with oesophageal cancer underwent resection at The General Infirmary at Leeds. Selection of patients for surgery was based on surgeons' 'end of the bed' assessment, supported by pulmonary function tests, arterial blood gas measurement, electrocardiography and, more recently, echocardiography. Ninety-two per cent of operations were performed by four consultants with a special interest in upper gastrointestinal surgery. Nine patients were excluded from the study owing to incomplete data despite extensive tracking of case notes. The remaining 204 patients were scored retrospectively using POSSUM, and the predicted risk of morbidity and death was calculated for each patient according to the following previously described logistic regression equations[5]:

$$\log_e[R_1/(1 - R_1)] = -5{\cdot}91 + (0{\cdot}16 \times \text{physiological score}) + (0{\cdot}19 \times \text{operative severity score})$$

where R_1 = risk of morbidity;

$$\log_e[R_2/(1 - R_2)] = -7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative severity score})$$

where R_2 = risk of death.

The definitions and classification of morbidity have been described previously[5] and mortality was determined at 30 days.

Statistical analysis

The performance of POSSUM in predicting mortality and morbidity was analysed by measures of calibration and discrimination[12]. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and the corresponding calibration curves[13]. The patients were divided into risk groups on the basis of their predicted mortality and morbidity. The observed and predicted numbers of patients who experienced the event (death or complication) and those who did not were determined for each risk group. Summing the probabilities of mortality or morbidity for all patients in a risk group produced the predicted number of deaths or complications in that risk group. The discrepancies between the observed and predicted outcomes in these groups were tested using the χ^2 goodness-of-fit test. In this test $P > 0{\cdot}05$ indicates that the model is performing well.

Model discrimination was assessed using the area under the receiver–operator characteristic (ROC) curve (AUC)[14] to evaluate how well the model distinguished patients who experienced the event (death or complication) from those who did not. This statistic represents the concordance between predicted probabilities and observed outcomes for all possible pairs of patients with different outcome status. The AUC is used as an index of model discrimination; it ranges from 0·5 for chance performance to 1·0 for perfect prediction. In all analyses, confidence intervals were chosen at 95 per cent and $P < 0{\cdot}05$ was considered significant.

Results

Two hundred and four patients were scored; 146 (71·6 per cent) were men and the median age was 66 (range 29–89) years. More than three-quarters of patients underwent an Ivor–Lewis oesophagectomy; the remainder had a transhiatal or McKeown oesophagectomy. One-quarter of patients developed respiratory infection, 8 per cent had a wound infection, 3 per cent suffered a myocardial infarct and 1 per cent a pulmonary embolus. Gastrografin (Schering Health Care, Burgess Hill, UK) swallow was routinely performed on the seventh day after operation; an anastomotic leak was detected in less than 10 per cent. The median physiological score assigned by POSSUM was 16 (range 12–33) and the median operative severity score was 19 (range 14–34).

Validation of the POSSUM mortality equation

Twenty-six patients (12·7 per cent) died within 30 days following operation compared with a predictive value of 39 (19·1 per cent), giving a standardized mortality ratio of 0·66 (95 per cent confidence interval (c.i.) 0·43 to 0·97). However, the Hosmer–Lemeshow goodness-of-fit test indicated that the POSSUM mortality equation had a significant lack of fit with the data (χ^2 = 16·26, 4 d.f., P = 0·002) (*Table 1*). The calibration curve for the POSSUM mortality equation applied to the data showed a discrepancy between actual and predicted mortality rates,

Table 1 Hosmer–Lemeshow goodness-of-fit test for the POSSUM mortality equation

Predicted risk of death (%)	No. of patients	No. of survivors		No. of deaths	
		Observed	Predicted	Observed	Predicted
> 0 to ≤ 10	56	53	51	3	5
> 10 to ≤ 20	83	70	71	13	12
> 20 to ≤ 30	33	28	25	5	8
> 30 to ≤ 40	14	11	9	3	5
> 40 to ≤ 50	9	8	5	1	4
> 50 to ≤ 100	9	8	4	1	5
> 0 to ≤ 100	204	178	165	26	39

POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. χ^2 = 16·26, 4 d.f., P = 0·002 especially in the moderate- and high-risk groups (*Fig. 1*). ROC curve analysis revealed that POSSUM had a poor discriminatory capability for death with a ROC curve close to the diagonal line of chance (AUC = 0·62 (95 per cent c.i. 0·52 to 0·71)) (*Fig. 2*).

Validation of the POSSUM morbidity equation

Postoperative complications developed in 109 patients (53·4 per cent) compared with a predictive value of 127 (62·3 per cent), giving a standardized morbidity ratio of 0·86 (95 per cent c.i. 0·70 to 1·03). The Hosmer–Lemeshow goodness-of-fit test indicated that the POSSUM morbidity equation did not fit the data well ($\chi^2 = 63{\cdot}14$, 6 d.f., $P < 0{\cdot}001$) (*Table 2*). The calibration curve showed a discrepancy between the actual and predicted morbidity rates (*Fig. 3*). ROC curve analysis revealed that POSSUM had poor discriminatory power for morbidity (AUC = 0·55 (95 per cent c.i. 0·47 to 0·63)) (*Fig. 4*).

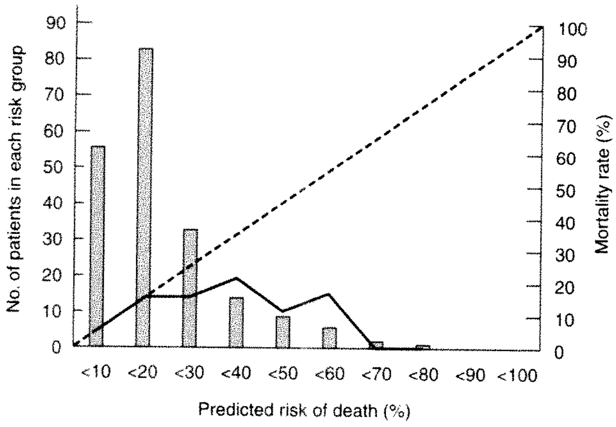

Fig. 1 Calibration curve for surgical mortality. The curve represents the proportion of patients dying within 30 days following operation according to their predicted risk of death estimated by the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) mortality equation. The dashed diagonal line represents the perfect predictive ability when observed and predicted mortality are equal

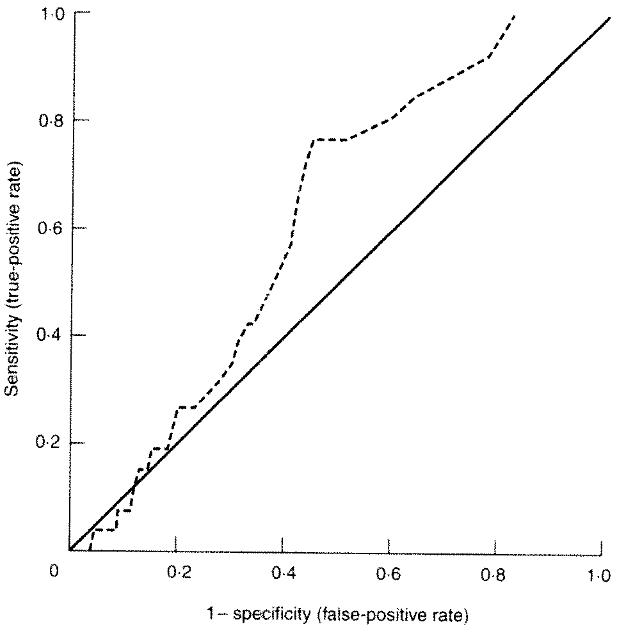

Fig. 2 Receiver–operator characteristic curve for mortality. The diagonal line represents predictive accuracy no better than chance. Area under the curve 0·62 (95 per cent confidence interval 0·52 to 0·71)

Table 2 Hosmer–Lemeshow goodness-of-fit test for the POSSUM morbidity equation

Predicted risk of morbidity (%)	No. of patients	No. of survivors		No. of deaths	
		Observed	Predicted	Observed	Predicted
> 0 to ≤ 30	4	3	3	1	1
> 30 to ≤ 40	26	11	17	15	9
> 40 to ≤ 50	26	14	14	12	12
> 50 to ≤ 60	47	28	21	19	26
> 60 to ≤ 70	33	11	11	22	22
> 70 to ≤ 80	28	12	7	16	21
> 80 to ≤ 90	24	9	3	15	21
> 90 to ≤ 100	16	7	1	9	15
> 0 to ≤ 100	204	95	77	109	127

POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. $\chi^2 = 63{\cdot}14$, 6 d.f., $P < 0{\cdot}001$

Comparison of patients who died within 30 days with survivors

To investigate whether factors other than those recorded by POSSUM were significant in determining outcome, patients who died within 30 days of surgery were compared with those who survived longer. There were no significant differences in sex, tumour type, site and stage, type and completeness of resection, and use of neoadjuvant treatment between the two groups. Interestingly, there were no significant differences in POSSUM score for patients who died compared with survivors (*Table 3*).

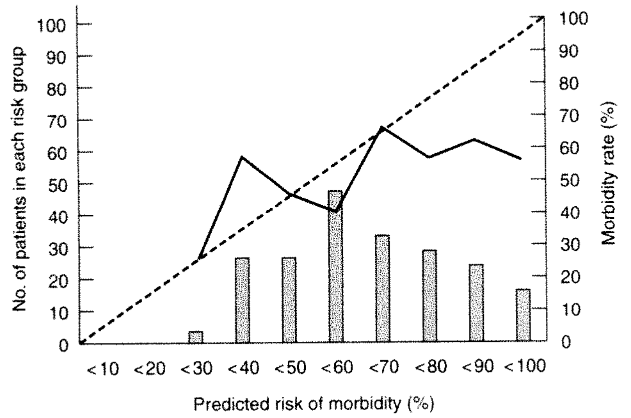

Fig. 3 Calibration curve for surgical morbidity. The curve represents the proportion of patients with complications following operation according to their predicted risk of morbidity estimated by the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) morbidity equation. The dashed diagonal line represents the perfect predictive ability when observed and predicted morbidity are equal

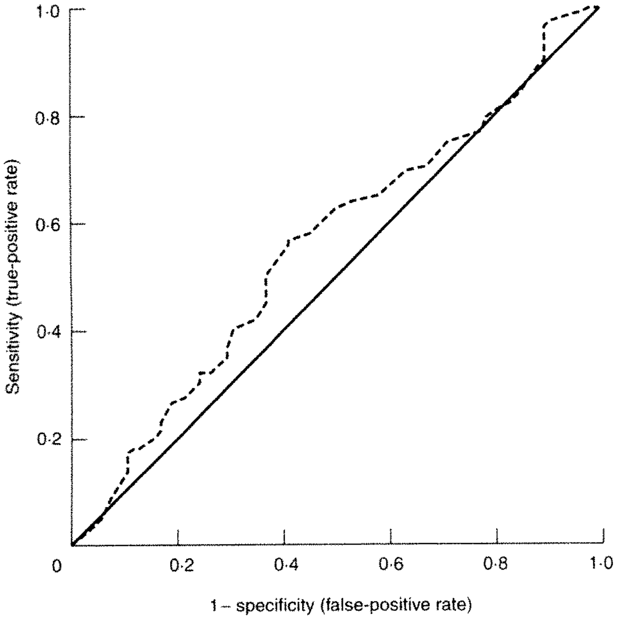

Fig. 4 Receiver–operator characteristic curve for morbidity. The diagonal line represents predictive accuracy no better than chance. Area under the curve 0·55 (95 per cent confidence interval 0·47 to 0·63)

Discussion

Before introduction to clinical practice, risk prediction models must be validated in a patient population independent from the population in which they were generated. Application of a model to a population with a different case

Table 3 Comparison of patients who died within 30 days and survivors

	Patients who died* (*n* = 26)	Survivors (*n* = 178)
Sex		
Male	19 (73·1)	127 (71·3)
Female	7 (26·9)	51 (28·7)
Tumour site		
Upper third	0 (0)	1 (0·6)
Middle third	7 (26·9)	38 (21·3)
Lower third	19 (73·1)	139 (78·1)
Histological type		
Adenocarcinoma	18 (69·2)	138 (77·5)
Squamous cell	8 (30·8)	37 (20·8)
Mixed	0 (0)	2 (1·1)
Oat cell	0 (0)	1 (0·6)
UICC stage		
I	3 (11·5)	25 (14·0)
IIA	8 (30·8)	39 (21·9)
IIB	3 (11·5)	18 (10·1)
III	9 (34·6)	67 (37·6)
IV	3 (11·5)	29 (16·3)
R category		
R0	14 (53·8)	85 (47·8)
R1	10 (38·5)	72 (40·4)
R2	2 (7·7)	21 (11·8)
Type of operation		
Ivor–Lewis	20 (76·9)	138 (77·5)
Transhiatal	0 (0)	9 (5·1)
McKeown	2 (7·7)	5 (2·8)
Thorascopically assisted	3 (11·5)	19 (10·7)
Left thoracoabdominal	1 (3·8)	7 (3·9)
Neoadjuvant treatment	4 (15·4)	35 (19·7)
POSSUM		
Mean (range) predicted mortality risk (%)	20·9 (9·2–52·1)	19·1 (4·3–72·2)
Mean (range) predicted morbidity risk (%)	69·2 (42·7–94·1)	61·4 (21·0–97·6)

Values in parentheses are percentages unless otherwise indicated. *Within 30 days. UICC, Union Internacional Contra la Cancrum; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. There were no significant differences between the two groups mix from the sample from which the model was derived may produce misleading outcome predictions[15]. Model validation should be performed using measures of calibration and discrimination[12], as these are complementary and provide different information about model performance[16]. This is the first study to evaluate POSSUM in estimating mortality and morbidity using measures of both calibration and discrimination.

Calibration evaluates the degree of correspondence between the estimated probabilities of mortality and morbidity produced by the model and the actual experience of patients in various risk strata[12]. Using the Hosmer–Lemeshow test[13], POSSUM showed a poor fit with the data for both mortality and morbidity. Across the risk categories POSSUM performed relatively well in low-risk groups of patients and overpredicted the number of deaths and complications in high-risk groups. Overall, POSSUM overpredicted mortality and morbidity rates in patients with oesophageal cancer undergoing resection.

Model discrimination evaluates the ability of the model to distinguish patients who will experience the event of interest (death or complication) from those who will not[12]. ROC curve analysis revealed that POSSUM had poor discriminative capability for both mortality and morbidity in patients undergoing oesophagectomy for cancer.

The published literature on POSSUM has focused on the use of the model as a tool for comparative surgical audit[7–11,17,18], and few independent studies have attempted validation of POSSUM. In general surgery the Hosmer–Lemeshow test revealed that POSSUM overpredicted overall risk of death, performing worst among low-risk general surgical patients[19,20]. In an attempt to improve the predictive ability of the POSSUM mortality equation the authors proposed a simple adjustment of the model using the same variables in a different formula (Portsmouth POSSUM). In vascular surgery a 'linear' type of analysis found that POSSUM predicted morbidity well but significantly overpredicted mortality[21]. Although none of these studies validated its chosen model by measures of both calibration and discrimination, they agree with this study that POSSUM overpredicts death.

The original paper describing POSSUM evaluated its overall performance in the general surgical population without reporting the uniformity of fit of the model across the various surgical subspecialties[5]. The poor performance of POSSUM in this study may be a reflection that the model was originally based on a general surgical population that contained few if any patients undergoing oesophagectomy, and the score assigned to oesophagectomy may be too high. Amendment of the operative severity score may increase the predictive value of POSSUM but a larger data set is required for this. With respect to the physiological score of patients undergoing oesophagectomy, POSSUM does not include variables such as arterial blood gases, pulmonary function tests and echocardiography. The introduction of these variables into the physiological equation may improve its predictive value.

POSSUM cannot be used to audit oesophagectomy for cancer because of overprediction of mortality and morbidity. To develop new equations for patients with oesophageal cancer undergoing resection, a national database of oesophageal resections is required, with physiological scores potentially including arterial blood gases, pulmonary function tests and echocardiography. Logistic regression analysis would determine a POSSUM model for patients with oesophageal cancer undergoing oesophagectomy and this model must be validated in an independent population by measures of both calibration and discrimination.

To describe surgical mortality and morbidity in a meaningful way, it is essential that an accurate method of comparing mortality and morbidity rates following oesophagectomy is developed as soon as possible.

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Original article

Surgical management of and long-term survival after adenocarcinoma of the cardia

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Background: The choice of surgical strategy for patients with adenocarcinoma of the oesophagogastric junction is controversial. This study was performed to analyse the surgical results of a 20-year experience with these lesions.

Methods: From January 1981 to January 2001, 126 patients with adenocarcinoma of the cardia underwent resection in the authors' institution. The treatment of choice was oesophagectomy for type I tumours, and extended gastrectomy for type II and III lesions. Morbidity, mortality and survival were determined retrospectively.

Results: Fifty-six patients (44·4 per cent) had type I tumours, 44 (34·9 per cent) type II and 26 (20·6 per cent) type III. Primary resection was performed in 113 patients (89·7 per cent). Oesophagectomy with resection of the proximal stomach was carried out in 65 patients (51·6 per cent) and extended total gastrectomy with transhiatal resection of the distal oesophagus in 61 (48·4 per cent). In-hospital mortality and morbidity rates were 4·8 and 34·1 per cent respectively. The overall 3- and 5-year survival rates were 40·9 and 25·1 per cent respectively, and were not affected by the surgical approach. Survival was significantly associated with R0 resection, pathological node-positive category, postoperative complications and tumour differentiation.

Conclusion: Postoperative mortality, morbidity and long-term survival did not appear to be affected by surgical approach. Further prospective studies are needed to confirm the equivalence between transthoracic and transabdominal approaches.

Paper accepted 8 May 2002

British Journal of Surgery 2002, 89, 1156–1163

Introduction

In contrast to gastric cancer, the incidence and prevalence of oesophageal carcinoma is rising at an alarming rate in the western world. This is primarily due to an increase in the rate of adenocarcinoma of the distal oesophagus[1,2]. In addition, there is a shift in the location of tumour from the distal portion of the stomach to the proximal stomach and the gastric cardia[3]. The treatment of adenocarcinoma arising at or close to the oesophagogastric junction will therefore become a major challenge in the coming years.

Although adenocarcinoma of the gastric cardia has often been considered together with either oesophageal or upper gastric tumours, it should be regarded as a separate neoplasm because it appears to have distinctive prognostic and pathological features[4]. Surgical treatment of the cardia is still controversial, mainly regarding the extent of gastric and oesophageal resection. After standard oesophagogastrectomy, the operative mortality rate in recent studies has ranged between 3·8 and 7·0 per cent, and the 5-year survival rate between 16·0 and 32·3 per cent[5–8]. This paper presents a 20-year experience with surgical management of adenocarcinoma of the cardia, with an analysis of operative mortality and morbidity rates, long-term results and prognostic factors, and an evaluation of surgical techniques.

Patients and methods

Patient population and classification

The records of 700 patients with carcinoma of the oesophagus operated on in the authors' department from 1 January 1981 to 1 January 2001 were reviewed. Among these were 126 patients (18·0 per cent) who underwent resection with curative intent for carcinoma of the cardia. Adenocarcinoma of the oesophagogastric junction was defined as a tumour whose centre was within 5 cm proximal and distal of the anatomical cardia[9]. Patients with systemic metastases on preoperative staging or poor general status precluding an extensive surgical procedure were excluded.

Based on the anatomical location of the tumour centre or, in patients with advanced tumours, the tumour mass, all tumours were retrospectively classified as follows[5]. Type I was adenocarcinoma of the distal oesophagus, usually arising from an area with specialized intestinal metaplasia of the oesophagus, perhaps infiltrating the oesophagogastric junction from above. Type II was a true adenocarcinoma of the cardia arising immediately at the oesophagogastric junction. Type III was subcardial gastric carcinoma infiltrating the oesophagogastric junction and distal oesophagus from below. The assignment was purely morphological and topographical, and based on the findings of contrast radiography, endoscopy, computed tomography and intraoperative findings. The surgical approach selected was based on this classification; type I tumours were treated as oesophageal cancer, and type II and III tumours as gastric cancer, from the start of the study.

The retrospectively collected data included demographic parameters, histomorphological tumour characteristics, the presence of associated intestinal metaplasia in the distal oesophagus, the type of resection, postoperative 30-day mortality and morbidity rates, the depth of tumour invasion and the node category (according to the pathological tumour node metastasis (pTNM) classification), and the presence of residual disease on intraoperative assessment and histopathological analysis of the resected specimen.

Surgical approach

The choice of surgical approach was based on the tumour type and the goal of achieving complete macroscopic and microscopic tumour resection. In general, radical transmediastinal or transthoracic *en bloc* oesophagectomy with resection of the proximal stomach was the procedure of choice in patients with type I tumours[10]. Extended total gastrectomy with transhiatal resection of the distal oesophagus was performed in patients with type III tumours[3]. In patients with type II tumours, an attempt was usually made to achieve complete tumour resection by means of extended gastrectomy associated with a transthoracic resection of the distal oesophagus, 6–10 cm above the tumour, and reconstruction with jejunal loop and oesophagojejunal anastomosis at the level of the azygos vein. If complete tumour resection appeared unlikely, based on the intraoperative findings, an extended gastrectomy with distal oesophagectomy by a transabdominal approach was performed.

A subgroup of patients with locally advanced tumours (computed tomography T3–4 Nx M0) underwent resection after neoadjuvant cisplatin-based chemotherapy.

Radical transmediastinal oesophagectomy and resection of the proximal stomach was performed by laparotomy and wide exposure of the lower posterior mediastinum by anterior splitting of the diaphragmatic hiatus and a left cervical incision. Lymphadenectomy comprised *en bloc* removal of all lymphatic tissue in the lower posterior mediastinum, in left and right paracardial regions, in suprapyloric and infrapyloric sites, along the lesser and greater curvatures, and along the left gastric artery.

A transthoracic *en bloc* oesophagectomy with resection of the proximal stomach was performed using a right posterolateral thoracotomy and laparotomy, and included an extended *en bloc* mediastinal lymphadenectomy and an abdominal lymphadenectomy (two-field lymphadenectomy). The abdominal lymphadenectomy was done as described above. Lymphadenectomy of the paratracheal, subcarinal, and left and right bronchial lymph nodes was performed with a fifth interspace thoracotomy and was followed by *en bloc* resection of the thoracic duct with the para-aortic lymph nodes. Reconstruction after transmediastinal or transthoracic oesophagectomy was performed with a gastric tube or colonic interposition and a cervical or high thoracic anastomosis.

Extended total gastrectomy always included wide splitting of the diaphragmatic hiatus, transhiatal resection of the distal oesophagus, and *en bloc* lymphadenectomy of the lower posterior mediastinum, in addition to a formal D1,5 lymphadenectomy (lymph node stations 1–7 of the Japanese classification). Dissection of the splenic artery, the coeliac trunk, the left retroperitoneal para-aortic and left renal hilum nodes was performed only in patients who had enlarged nodes at these areas on preoperative or intraoperative staging. An end-to-side oesophagojejunostomy, transmediastinal or transthoracic, performed with a circular stapler or manually, and Roux-en-Y bile diversion was the procedure of choice after extended total gastrectomy.

Histopathological assessment of the removed specimen and lymph nodes

Resection specimens were assessed by an experienced pathologist. All removed lymph nodes were counted, assessed separately, and identified according to their location. Staging is reported according to the most recent version of the Union Internacional Contra la Cancrum–American Joint Committee on Cancer (UICC–AJCC) guidelines for oesophageal cancer (type I tumours) or gastric cancer (type II and III tumours)[11,12]. A particular effort was made to identify areas with intestinal metaplasia in the distal oesophagus and in the region of the cardia in all resection specimens.

Statistical analysis

The survival status of patients was ascertained in October 2001. Follow-up was complete for all 126 patients. Data are shown as prevalence or mean(s.d.). Continuous data were compared with the Mann–Whitney U test, and ordinal data with the χ^2 test. In analysing survival time, the Statistical Package for the Social Sciences (SPSS®, Chicago, Illinois, USA) was used. The survival function was estimated by the actuarial method without excluding the postoperative deaths. The log rank test was used for comparison of survival curves. $P < 0.05$ was considered statistically significant. Prognostic factors were analysed with a proportion hazard regression analysis according to Cox, using a stepwise procedure; the 0·2 level was defined for entry into the model. Multivariate χ^2 and P values were used to characterize the independence of these factors; the relative risk was used to quantify the relationship between survival time and each independent factor.

Results

Of the 126 patients with resected adenocarcinoma of the oesophagogastric junction, 56 (44·4 per cent) had type I tumours, 44 (34·9 per cent) had type II and 26 (20·6 per cent) had type III. The most common complaint at initial evaluation was dysphagia, in 77 patients (61·1 per cent). Weight loss (more than 10 per cent of physical weight) was present in 28 patients (22·2 per cent). Respiratory antecedents were respiratory insufficiency ($n = 18$), pneumonia ($n = 8$) and asthma ($n = 3$). A comparison of the demographic data and histomorphological tumour characteristics showed marked discrepancies between the three types. The preponderance of age less than 60 years ($P = 0.014$) and the prevalence of associated intestinal metaplasia in the distal oesophagus ($P = 0.006$) decreased from type I to type III tumours (*Table 1*).

Table 2 shows the distribution of surgical procedures. Primary resection was performed in 113 (89·7 per cent) of 126 patients, and 13 (10·3 per cent) underwent resection

Table 2 Surgical approaches used for the different tumour types

	Total (n = 126)	Type I (n = 56)	Type II (n = 44)	Type III (n = 26)
Oesophagectomy				
Transthoracic	56 (44·4)	44 (78·6)	11 (25·0)	1 (3·8)
Transmediastinal	9 (7·1)	7 (12·5)	0 (0·0)	2 (7·7)
Extended gastrectomy				
Transhiatal anastomosis	41 (32·5)	1 (1·8)	20 (45·5)	20 (76·9)
Intrathoracic anastomosis	20 (15·9)	4 (7·1)	13 (29·5)	3 (11·5)

Values in parentheses are percentages

Table 1 Demographic and morphological tumour characteristics

	Total (n = 126)	Type I (n = 56)	Type II (n = 44)	Type III (n = 26)	P
Mean(s.d.) age at presentation (years)	60·6(10·7)	60·0(9·9)	58·7(10·2)	65·1(12·2)	0·014
Sex ratio (M : F)	6·4 : 1	7·0 : 1	10·0 : 1	3·3 : 1	0·244
ASA score					
1	41 (32·5)	22 (39·3)	13 (29·5)	6 (23·1)	0·440
2	61 (48·4)	26 (46·4)	21 (47·7)	14 (53·8)	
3	24 (19·0)	8 (14·3)	10 (22·7)	6 (23·1)	
Respiratory antecedent					
No	97 (77·0)	43 (76·8)	35 (79·5)	19 (73·1)	0·824
Yes	29 (23·0)	13 (23·2)	9 (20·5)	7(26·9)	
Weight loss					
< 10 per cent	98 (77·8)	43 (76·8)	35 (79·5)	20 (76·9)	0·957
≥ 10 per cent	28 (22·2)	13 (23·2)	9 (20·5)	6 (23·1)	
Prevalence of associated intestinal metaplasia in distal oesophagus (Barrett oesophagus)	29 (23·0)	14 (25·0)	10 (22·7)	5 (19·2)	0·006
Tumour differentiation					
Well	58 (46·0)	26 (46·4)	21 (47·8)	11 (42·3)	0·330
Moderate	34 (27·0)	12 (21·4)	14 (31·8)	8 (30·8)	
Poor	21 (16·7)	11 (19·6)	6 (13·6)	4 (15·4)	
Not applicable	13 (10·3)	7 (12·5)	3 (6·8)	3 (11·5)	

Values in parentheses are percentages, unless stated otherwise. ASA, American Society of Anesthesiologists after neoadjuvant polychemotherapy. Oesophagectomy (transthoracic or transmediastinal) with resection of the proximal stomach was the primary procedure in patients with type I tumours (91·1 per cent); extended total gastrectomy with transhiatal resection of the distal oesophagus was performed in 23 of 26 patients with type III tumours. In patients with type II tumours, an extended gastrectomy associated with a transthoracic resection of the distal oesophagus and intrathoracic oesophagojejunal anastomosis was the surgical approach of choice in curative cases (13 of 44 patients), while an extended gastrectomy with intra-abdominal oesophagojejunal anastomosis was the preferred method in palliative cases (20 of 44 patients).

Postoperative mortality

The overall postoperative 30-day death rate was 3·9 per cent. The in-hospital mortality rate was 4·8 per cent. Causes of death were anastomotic leak ($n = 2$), pneumonia and respiratory failure ($n = 1$), pancreatitis ($n = 1$), cardiac infarction ($n = 1$) and mesenteric infarction ($n = 1$). The surgical approach did not influence postoperative mortality ($P = 0{\cdot}164$).

Postoperative morbidity

Significant complications occurred in 43 patients (34·1 per cent). Eleven (8·7 per cent) anastomotic leaks were observed clinically or radiologically. Respiratory complications were observed in 27 patients (21·4 per cent). No factors were observed that influenced postoperative morbidity significantly. The mean(s.d.) time to resumption of oral feeding was 10·1(5·0) (range 6–34) days after operation. The mean(s.d.) hospital stay for the whole population was 14·6(8·0) (range 4–55) days: 13·9(6·4) (range 9–45) days for type I tumours, 14·7(7·4) (range 6–41) days for type II and 15·8(4·4) (range 6–25) days for type III tumours (P not significant).

Histopathological analysis

On histopathological assessment of the resected specimens, the distribution of pT and pN categories was homogeneous between the three groups. The lesion was restricted to either the mucosa or submucosa in 21 cases (16·7 per cent), restricted to the muscularis propria in 27 cases (21·4 per cent), invaded the adventitia in 71 cases (56·3 per cent) and invaded the neighbouring structures in seven cases (5·6 per cent). Lymph node metastases were found in 88 patients (69·8 per cent): in 38 patients with type I cancer, in 31 with type II and in 19 with type III. A mean(s.d.) of 14·5(11·2) (range 1–72) lymph nodes was dissected from each specimen by the surgeon and pathologist. The mean(s.d.) number of histopathologically positive lymph nodes was 3·3(4·4) (range 0–21). In the abdomen, the most frequent sites of nodal metastasis were the right (51·0 per cent of patients), the left paracardial (45·0 per cent) and the left gastric (49·0 per cent) regions, whereas the paraoesophageal and para-aortic (49·0 per cent) were most often positive within the mediastinum.

Curative resection (R0) was performed in 89 patients (70·6 per cent). Of these, 43 patients had type I cancer, 33 had type II and 13 had type III. There was a higher R0 resection rate in patients with type I tumours than in those with type II or III lesions ($P = 0{\cdot}034$). Tumour-free resection margins were achieved in 108 patients (85·7 per cent). The distribution of this parameter was homogeneous between the three groups ($P = 0{\cdot}21$). On the other hand, microscopic neoplastic invasion of the resection margin was significantly higher in patients who underwent extended total gastrectomy and resection of the distal oesophagus (6·6 per cent) than in those who underwent oesophagectomy with proximal gastric resection (23·7 per cent) ($P = 0{\cdot}008$). There was a survival advantage for patients with well or moderately differentiated carcinomas compared with patients with poorly differentiated carcinomas ($P = 0{\cdot}033$).

Actuarial survival

Follow-up was complete for all 126 patients. The mean(s.d.) follow-up was 30·3(35·1) (range 6–228) months. The overall 3- and 5-year survival rates for the entire population of 126 patients with resected adenocarcinoma of the oesophagogastric junction were 40·9 and 25·1 per cent respectively, with a median survival time of 23·9 months. On multivariate analysis, complete macroscopic and microscopic tumour resection (R0 resection, $P < 0{\cdot}001$), pN category ($P < 0{\cdot}001$), postoperative complications ($P = 0{\cdot}009$) and tumour differentiation ($P = 0{\cdot}024$) were the prominent independent prognostic factors (*Table 3*). The location of the primary tumour was not an independent prognostic factor ($P = 0{\cdot}4$).

The 3- and 5-year survival rates for patients who underwent extended total gastrectomy and resection of the distal oesophagus were 37·3 and 18·4 per cent respectively. They were similar to those in patients who underwent oesophagectomy with proximal gastric resection, 44·1 and 31·9 per cent respectively ($P = 0{\cdot}53$).

Patients with negative lymph nodes (N0; $n = 38$) had 3- and 5-year survival rates of 82·7 and 70·1 per cent respectively, whereas those with positive lymph nodes (N+ $n = 88$) had respective survival rates of 24·2 and 8·1 per cent. The threshold value for the number of positive lymph nodes to have a significant influence on the overall 5-year survival

Table 3 Overall survival: prognostic parameters obtained from multivariate analysis

	P	d.f.	χ^2	Risk ratio
Complete resection (R0 *versus* R1–2)	< 0·001	1	12·3	3·5 (1·7, 7·1)
pN category	< 0·001	1	11·2	8·7 (2·4, 30·2)
Postoperative complications	0·009	1	6·8	3·0 (1·3, 6·9)
Tumour differentiation	0·024	1	5·1	1·7 (1·1, 2·7)

Values in parentheses are 95 per cent confidence intervals. R, resection, pN, pathological node

Table 4 Three- and 5-year survival rates according to tumour type

	Type I (n = 56)	Type II (n = 44)	Type III (n = 26)
Actuarial survival (%)			
3 years	46·8	42·1	26·3
5 years	28·2	25·7	17·5

rate was five. Invasion of five or more lymph nodes was associated with a 5-year survival rate of 0 per cent, compared with 11·7 per cent when fewer than five lymph nodes were positive (P = 0·009).

The 3- and 5-year survival rates in patients with an R0 resection were 52·1 and 33·0 per cent respectively, compared with 15·2 and 0 per cent in patients with a R1–2 resection. The 3- and 5-year survival rates of patients with an R0 resection were not significantly different between the three types of tumour (P = 0·65), while there was a significantly higher R0 resection rate in patients with type I tumours.

The 3- and 5-year survival rates according to the tumour type are shown in *Table 4*. Tumour type did not influence actuarial survival (P = 0·2). In patients with type II tumours (n = 44), there were no significant differences in the distribution of pT, pN and R categories between those who underwent oesophagectomy with proximal gastric resection and those who had extented total gastrectomy with transhiatal resection of the distal oesophagus. Multivariate analysis of prognostic factors in this subgroup of patients identified only postoperative complications (P = 0·07) as an independent predictor of long-term survival. Of patients with type II tumours who had R0 resection, there was no significant difference in long-term survival between those who underwent oesophagectomy with proximal gastric resection and those who had extended total gastrectomy and transhiatal resection of the distal oesophagus (P = 0·53).

Discussion

Despite a rising incidence, there are marked discrepancies in the definition of adenocarcinoma of the oesophagogastric junction, the selection of the surgical approach and the outcome of surgical therapy[6,7,13–21].

Tumour classification

The authors' surgical approach was determined by the classification of Siewert *et al.*[5]. Although this classification is based purely on anatomical and topographic parameters, many analyses[5,22,23] have shown that it provides a useful tool to differentiate tumour entities arising in the vicinity of the oesophagogastric junction, and thus helps in selection of the surgical approach. Type I tumours clearly constitute a distinct entity that requires a specific therapeutic approach as distal oesophageal cancer. Most, if not all, of these tumours arise from areas with intestinal metaplasia in the distal oesophagus. Similarly, type III tumours clearly represent a special form of proximal gastric cancer and require treatment according to the well established gastric cancer guidelines. The relation of type II tumours to distal oesophageal or proximal gastric cancer, however, remains controversial.

Surgical approach

The surgical approach was not associated with any difference in hospital death or in the frequency of complications (P = 0·164). The number of patients undergoing a transthoracic approach was high in the authors' experience (44·4 per cent) and the patients were not randomized, making definitive conclusions difficult. However, it has been shown for carcinoma of the oesophagus in randomized trials that no difference in morbidity or mortality can be demonstrated between a transhiatal and a transthoracic approach[24–27]. The present study also found that long-term survival was unaffected by surgical approach. The arguments for and against the transhiatal approach are well documented for the treatment of oesophageal cancer[16,24,25,28,29]. Some authors[30,31] have argued in favour of thoracotomy for distal oesophageal tumours in order to allow a radical *en bloc* dissection to be performed. Moreover the relatively high incidence of positive resection margins is a cause of concern. Like the present authors, several investigators have postulated that 6–10 cm of macroscopically tumour-free oesophagus in the resected specimen is required to ensure a negative microscopic margin[20,32–34]. Several reports have suggested that surgery involving thoracotomy is associated with considerable respiratory complications[18,29] and wound pain[21]. This has led many surgeons to favour the transhiatal approach for lower oesophageal cancer resection on the grounds that the survival benefit from the extended lymphadenectomy in advanced disease is outweighed by the added morbidity associated with thoracotomy[35]. This argument is not, however, relevant for cardia tumours. The present results suggest that total radical gastrectomy via the transthoracic approach for patients with tumours at the gastric cardia is a relatively short operation associated with few postoperative complications and low levels of postoperative dependency.

Long-term survival

The long-term survival with adenocarcinoma of the cardia, even in patients selected for surgical resection, remains poor. In this study the overall 5-year survival rate was 25·1 per cent. Other studies have reported 5-year survival rates of 16·0–32·3 per cent[5–8]. Clearly, strategies such as surgery and radiotherapy directed at local control, although important, are not sufficient. A systemic approach is needed in addition to surgical resection. The present authors limit neoadjuvant therapy to patients with locally advanced tumours – those in whom, based on preoperative staging, a R0 resection appears questionable[36]. Walsh and colleagues[13] reported the results of a randomized clinical trial that compared preoperative chemotherapy and radiotherapy followed by surgery with surgery alone for adenocarcinoma of the oesophagus. Thirty-four per cent of patients enrolled in the study had adenocarcinoma of the cardia. Walsh *et al.* reported a median survival of 16 months for the multimodal group and 11 months for the group treated by surgery alone. In this study, the survival rate in the surgery-alone arm was, however, markedly worse than that reported previously from various expert centres for primary resection and extensive lymph node dissection. Although the median survival in the present study was 23·9 months, the prognosis remains poor, and scientific evaluation of new multimodal techniques is indicated.

Prognostic factors

In patients without systemic metastasis or peritoneal carcinosis, a complete tumour resection (R0) constitutes the most powerful independent prognostic factor[36], with a relative risk of 3·5 (95 per cent c.i. 1·7 to 7·1) ($P < 0·001$) in the present series. The chance of achieving complete tumour resection with primary surgery is clearly dependent on the tumour location and pT category. In the group of patients with a complete tumour resection, the lymph node status and the number of positive lymph nodes represent the major independent prognostic factor[36], with a relative risk of 8·7 (95 per cent c.i. 2·4 to 30·2) ($P < 0·001$) in the authors' hands. Because of the lack of well designed, controlled studies, the benefits, risks and optimal extent of lymphadenectomy for adenocarcinoma of the oesophagogastric junction are still controversial issues. Some authors[37,38] of recent prospective randomized studies have demonstrated no survival advantage for more radical lymphadenectomy in gastric carcinoma. Nevertheless, several studies have indicated that extended abdominal lymphadenectomy may improve survival in the group of patients with a limited number of positive lymph nodes or lymph node micro-involvement[39]. Like some others[8], the present authors think that, for cardia tumours progressing above the junction, there may be a role for more extensive mediastinal lymphadenectomy. It is well recognized that in Europe and North America oesophageal and gastric cancers occur late, with over two-thirds of patients having lymph node metastases at the time of operation[5]. However, despite these advances in lymphadenectomy, scepticism about its contribution to overall survival lingers among the scientific community; the present authors agree with the necessity of extended lymphadenectomy and believe that lymph node metastases signify the presence of systemic disease. The potential benefit of extended lymphadenectomy may, however, be nullified if there is an associated increase in postoperative morbidity. Finally, tumour differentiation was a prognostic parameter with an inferior prognosis in undifferentiated tumour with a relative risk of 1·7 (95 per cent c.i. 1·1 to 2·1) ($P = 0·024$). The undifferentiated type was not found to be more common than type III in the present series (19·6, 15·4 and 13·6 per cent for types I, II and III respectively) ($P = 0·65$), and this was also reported by Siewert *et al.*[5]. Therefore, Siewert *et al.* postulated that this finding is one of several epidemiological facts that provide justification for their classification, that is, that the topographic classification also correctly reflects the pathogenesis of the different types.

In conclusion, patients with adenocarcinoma of the cardia usually have a dismal prognosis and the tumour is often far advanced at diagnosis. A R0 resection should be performed to optimize the 5-year survival rate; the transthoracic approach seems to be a safe technique in the authors' experience, with no difference in terms of mortality, morbidity and long-term survival in comparison with the transhiatal approach. Further prospective randomized studies are needed to confirm the equivalence between these surgical approaches.

Acknowledgements

The authors acknowledge the careful and dedicated assistance of Dr I. Van Seuningen in reading this manuscript.

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Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer

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Background: Multiple organ metastases from colorectal carcinoma may be considered incurable, but long survival after both liver and lung resection for metastases has been reported.
Methods: A retrospective analysis of 48 patients who underwent lung resection for metastatic colorectal cancer between 1992 and 1999 was undertaken. Twenty-seven patients had lung metastasis alone, 15 had previous partial hepatectomy, and six had previous resection of local or lymph node recurrence. The relationship of clinical variables to survival was assessed. Survival was calculated from the time of first pulmonary resection.
Results: Five-year survival rates after resection of lung metastasis were 73 per cent in patients without preceding recurrence, 50 per cent following previous partial hepatectomy and zero after resection of previous local recurrence. Independent prognostic variables that significantly affected survival after thoracotomy were primary tumour histology and type of preceding recurrence. There was no significant difference in survival after lung resection between patients who had sequential liver and lung resection *versus* those who had lung resection alone.
Conclusion: Sequential lung resection after partial hepatectomy for metastatic colorectal cancer may lead to long-term survival.

Presented to the annual meeting of the Japan Surgical Society, Tokyo, Japan, April 2000
Paper accepted 29 April 2002
British Journal of Surgery 2002, **89**, 1164–1168

Introduction

A beneficial outcome after surgical resection of both liver and pulmonary metastases from colorectal cancer has been reported[1–4]. However, even after curative partial hepatectomy, further recurrence in the liver and lung metastasis often occur[5]. Lung metastases, previously thought to be incurable and treated mainly by systemic chemotherapy, may be amenable to curative resection in selected patients[6,7]. The outcome of lung resection for pulmonary metastasis following previous potentially curative liver resection is not known. In the present study, the results of lung resection following partial hepatectomy for pulmonary metastases from colorectal cancer were evaluated.

Patients and methods

Between April 1992 and December 1999, 48 patients underwent lung resection for pulmonary metastasis from colorectal cancer. Twenty-seven patients had lung metastasis alone (group 1), 15 had a history of previous partial hepatectomy for liver metastasis (group 2) and six had undergone resection of local or lymph node recurrence (group 3). In group 2, nine patients had had a solitary hepatic metastasis and six multiple hepatic metastases. Three patients had undergone more than one hepatectomy. In group 3, four patients had undergone resection of local recurrence and two had had lymph node dissection.

The strategy adopted for treating lung metastasis from colorectal cancer is shown in *Fig. 1*. If non-pulmonary recurrences were either absent or under control and lung metastases numbered fewer than five, resection of lung metastases was carried out as soon as possible. If the lung was the first and only site of recurrence and the metastasis was solitary, aggressive resection such as lobectomy was carried out with the aim of preventing local recurrence in the lung. If the lung metastasis represented only a portion of systemic disease, limited surgery such as partial resection was carried out to promote the quality of life after resection. Five patients underwent repeated lung resections. Forty patients received postoperative adjuvant chemotherapy. The most frequently used regimen consisted of eight cycles of 5-fluorouracil 750 mg/day and leucovorin 21 mg/day every 1 or 2 weeks, combined with oral tegafur or doxifluridine (21 patients).

Statistical analysis

Survival curves were derived using the Kaplan–Meier method, and univariate and multivariate analyses of survival were performed using SPSS8·0J software (SPSS Japan, Tokyo, Japan). $P < 0{\cdot}05$ indicated statistical significance.

Results

There were 29 men and 19 women with a mean age of 62 (range 32–84) years at the time of first pulmonary resection. Fifty-nine pulmonary resections were performed in 48 patients and 19 partial hepatectomies were carried out in 15 patients. Age, gender, primary site, histological differentiation of the primary lesion, disease-free interval, number of lung metastases and operative procedure are presented in *Table 1*. Overall median follow-up was 40 (range 0–113) months. Perioperative death occurred in one patient because of pulmonary embolism.

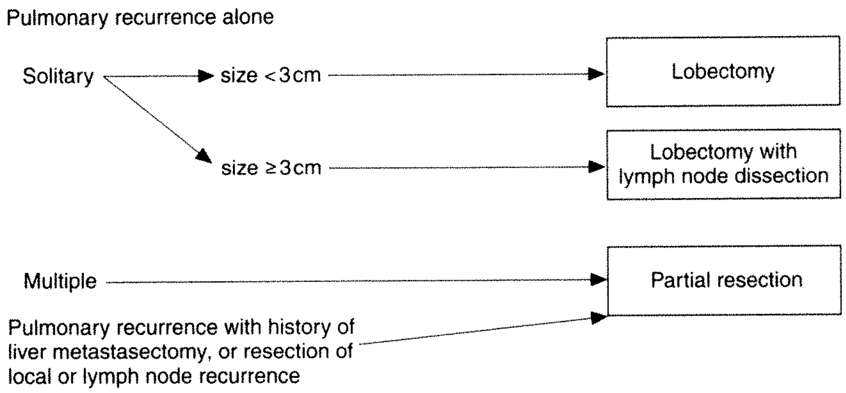

Pulmonary recurrence alone
Solitary
size <3cm
size ≥3cm
Lobectomy
Lobectomy with lymph node dissection
Multiple
Partial resection
Pulmonary recurrence with history of liver metastasectomy, or resection of local or lymph node recurrence

Fig. 1 Choice of operation for lung metastasis from colorectal cancer

Table 1 Patient characteristics

	Group 1	Group 2	Group 3
No. of patients	27	15	6
Age (years)*	61·4 (41–84)	61·6 (32–80)	63·7 (46–73)
Gender			
Male	15	9	5
Female	12	6	1
Primary site			
Colon	9	7	1
Rectum	18	8	5
Histology of primary lesion			
Well differentiated	15	10	3
Moderately differentiated	10	5	3
Poorly differentiated	1	0	0
Mucinous	1	0	0
No. of lung metastases			
1	19	8	2
2	4	4	2
3	2	1	1
4	2	0	1
5	0	2	0
Disease-free interval (months)*	30·3 (11–76)	35·3 (0–115)	25·5 (0–54)
Operative procedure			
Partial resection	6	10	2
Lobectomy	21	5	4

*Values are mean (range). Group 1, patients with pulmonary metastasis alone; group 2, patients with a history of previous hepatic resection; group 3, patients with a history of previous local or lymph node recurrence

Overall survival rate

The overall cumulative 5-year survival rate following resection of pulmonary metastases was 56 per cent. Seventeen patients died during follow-up. Metastatic cancer was the cause of death in 15 patients. Nine patients were alive with disease, while 22 patients were alive and free from disease after a median of 53 (range 19–100) months.

Prognostic factors after resection

Factors found significantly to affect survival by univariate analysis were histology of the primary tumour and presence of preceding metastasis (*Table 2*). The 5-year survival rate was 71 per cent in patients with well differentiated adenocarcinoma, 32 per cent in those with moderately differentiated adenocarcinoma and zero in patients with poorly differentiated adenocarcinoma or mucinous carcinoma. Gender, primary site, tumour size, number of metastatic lesions, histology of metastatic lesions, lymph node disease or type of lung resection had no significant influence on survival. By multivariate analysis, histology of the primary lesion (*P* = 0·013) and previous metastasis (*P* = 0·038) remained independent prognostic factors (*Table 2*).

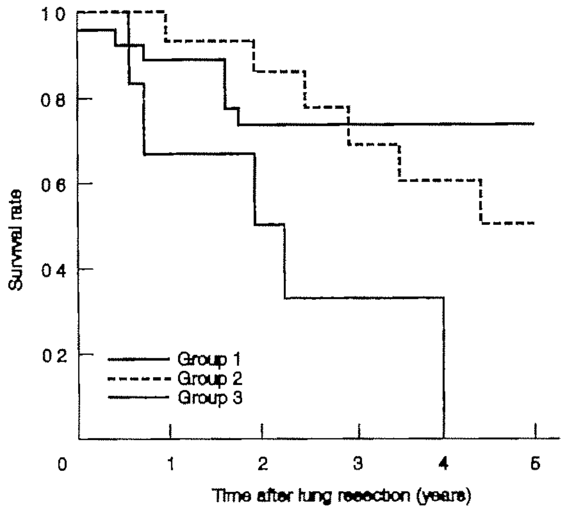
Survival rates according to previous recurrence

Cumulative survival following resection of pulmonary metastases from colorectal cancer according to the preced-

Table 2 Univariate and multivariate analysis in 48 operated patients with lung metastasis from colorectal cancer

	Univariate analysis				Multivariate analysis		
	No. of patients	5-year survival (%)	χ^2	*P*	Hazard ratio	χ^2	*P*
Age			0·20	0·658			
Gender			0·48	0·487			
Female	19	52					
Male	29	59					
Site of primary lesion			0·13	0·717			
Colon	17	59					
Rectum	31	69					
Histology of primary lesion			10·70	0·014		10·75	0·013
Well differentiated	28	71			21·23 (2·08, 216·26)		
Moderately differentiated	18	32			1		
Poorly differentiated	1	0			0·00		
Mucinous	1	0			4·28 (1·47, 12·42)		
No. of metastatic lesions			2·25	0·134			
1	29	63					
2	10	57					
3	4	0					
4	3	0					
5	2	100					
Size of metastatic lesion			1·08	0·300			
Histology of metastatic lesion			0·12	0·942			
Well differentiated	20	46					
Moderately differentiated	26	63					
Mucinous	2	0					
Hilar or mediastinal lymph node metastasis			1·20	0·158			
No	45	57					
Yes	3	33					
Disease-free interval*			1·37	0·242			
Previous recurrence			7·87	0·020		6·57	0·038
Group 1	27	73			0·29 (0·08, 0·98)		
Group 2	15	50			1		
Group 3	6	0			0·20 (0·56, 0·73)		
Operation			0·60	0·440			
Lobectomy	30	61					
Partial resection	18	50					

Values in parentheses are 95 per cent confidence intervals. *Disease-free interval from resection of primary tumour. Group 1, patients with pulmonary metastasis alone; group 2, patients with a history of previous hepatic resection; group 3, patients with a history of previous local or lymph node recurrence



No. at risk	0	1	2	3	4	5
Group 1	27	24	17	14	11	7
Group 2	15	14	12	9	7	3
Group 3	6	4	3	1	0	0

Fig. 2 Cumulative survival curves after lung resection according to the preceding recurrence. Group 1, patients with pulmonary metastasis alone; group 2, patients with a history of previous hepatic resection; group 3, patients with a history of previous local or lymph node recurrence. $P = 0{\cdot}570$ (group 1 *versus* group 2); $P = 0{\cdot}014$ (group 1 *versus* group 3); $P = 0{\cdot}013$ (group 2 *versus* group 3) (log rank test)

ing recurrence is shown in *Fig. 2*. The 5-year survival rate and mean survival time were 73 per cent and 48 months in group 1, 50 per cent and 48 months in group 2, and zero and 28 months in group 3. There was no significant difference between group 1 and group 2. Seven patients in group 2 were alive without disease after a median of 72 (range 25–100) months.

Discussion

After curative resection of colorectal cancer, 30–40 per cent of patients develop metastatic lesions at various sites such as liver, lung, pelvis, lymph node, peritoneum, bone and brain[8,9]. Surgical resection of liver and lung metastases may be more effective than resection of recurrences at other sites. The 5-year survival rate after partial hepatectomy for liver metastasis is between 30 and 50 per cent[3,4]. Some authors have adopted an aggressive policy of hepatic resection even in patients with multiple metastases[10,11]. The 5-year survival rate following resection of lung metastasis is reported to be 40 per cent in selected patients[1,2].

Sugihara *et al.*[5] noted that late recurrence after curative resection for liver metastasis most commonly occurred in the liver and the lung. Five-year survival rates after sequential resection of hepatic and pulmonary metastases have been reported as 11 per cent by Regnard *et al.*[12], 31 per cent by Kobayashi *et al.*[13] and 44 per cent by Murata *et al.*[14]. The present study evaluated the efficacy of lung resection for colorectal cancer metastasis following partial hepatectomy for liver metastasis.

The choice of surgical procedure for treating pulmonary metastases is unresolved. Ballantine *et al.*[15] reported that the metastatic tumour recurred at or near the site of pulmonary wedge resection in half of patients. Partial resection by video-assisted thoracic surgery has become popular in treating patients with metastatic lung cancer[16,17]. However, no data are available regarding outcomes of partial resection compared with lobectomy in patients with lung metastasis. Lobectomy was performed in patients with a solitary pulmonary metastasis in the present series even when the tumour diameter was less than 3 cm, with the objective of preventing local recurrence in the lung. Cahan[18] advocated lobectomy for metastatic lesions because of a large number of secondary regional lymph node metastases. Lymph node dissection was added when the metastasis exceeded 3 cm in diameter, since Nakagawa *et al.*[19] reported a frequency of lymph node metastasis of only 8 per cent when the metastasis measured 3 cm or less, but of 50 per cent or more when the metastasis exceeded 3 cm in diameter. Only one of three patients with lymph node involvement was still alive without recurrence 6 years after pulmonary resection. The other two patients with mediastinal lymph node involvement developed brain and bone metastasis soon after lung resection.

Partial resection was carried out in patients with multiple lung metastases and those with a history of resection of a previous liver or local recurrence. In these patients further recurrence was expected, but preservation of pulmonary function was considered important for maintaining quality of life. Even though partial resection was used to treat lung metastasis in patients with a previous partial hepatectomy, the 5-year survival rate reached 50 per cent, and was not significantly different from that in patients with lung metastasis alone. Thus, resection of pulmonary metastasis from colorectal cancer may result in cure even after partial hepatectomy for liver metastasis. This observation indicated that partial resection might be a feasible procedure in selected patients with lung metastasis alone. Indications for partial resection to treat solitary pulmonary metastasis in patients with colorectal cancer have not been determined, but should be developed in the near future.

The outcome following resection of local recurrence is poorer than that after resection of liver and lung recurrence[20,21]. Local control is a key consideration in resection of distant metastasis. In the present study, the results of resection of pulmonary metastasis following resection for local or lymph node recurrence were dismal.

Adjuvant therapy using hepatic arterial infusion has been noted to be effective in improving surgical outcome following curative liver resection[22,23]. However, the efficacy of adjuvant chemotherapy after lung resection for metastasis from colorectal cancer has not been considered. The response rate of chemotherapy using doxifluridine and mitomycin C in patients with inoperable lung metastases was reported as only 9 per cent[24]. However, patients who have undergone pulmonary resection for metastases should be offered adjuvant chemotherapy for prevention of subsequent recurrence.

Prognostic factors after sequential resection of hepatic and pulmonary metastases include serum concentration of carcinoembryonic antigen, disease-free interval, and the number of lung and hepatic metastases. While Murata *et al.*[14] reported that time of appearance of metastasis and distribution of pulmonary metastases influenced survival independently, histological differentiation of the primary lesion was a prognostic factor after sequential resection of hepatic and pulmonary metastases in the present study. Pulmonary metastases from well differentiated adenocarcinomas of the colon and rectum are good candidates for resection.

In conclusion, sequential lung resection for metastatic colorectal cancer may result in long-term survival even following partial hepatectomy.

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Original article

Clinical experience in continuous graft monitoring with microdialysis early after liver transplantation

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Background: Early detection of impaired graft function after transplantation is essential. Microdialysis permits continuous monitoring of metabolic changes by mimicking the passive function of a capillary blood vessel by perfusion of a tubular semipermeable membrane introduced into the tissue. Based on the results of animal experiments, a clinical pilot study was undertaken.

Methods: Ten consecutive patients undergoing whole-organ orthotopic liver transplantation were studied. Intrahepatic implantation of a microdialysis catheter was performed at the end of the operation. A reference catheter was placed in the subcutaneous tissue over the right pectoral area immediately after abdominal closure. Consecutive serial samples were collected at 1-h intervals for 3 days after the operation. Glucose, lactate, pyruvate and glycerol concentrations were measured.

Results: During the first 24 h, the glucose level was higher in the liver than in reference tissue. Initially, increased mean(s.e.m.) levels of lactate (7·0(1·9) mmol/l) were observed in the liver, with a rapid decrease (to 2·7(0·3) mmol/l) over 24 h. A decrease in, and later stabilization of, the lactate : pyruvate ratio in the liver, from 18·7(4·2) to 10·0(1·1), was observed within 24 h after transplantation. Liver glycerol levels decreased from 62·3(7·4) to 24·3(7·5) μmol/l within the first 16 h after reperfusion and remained stable thereafter.

Conclusion: Microdialysis allows continuous monitoring of tissue metabolism in the transplanted liver. The procedure is easy to perform and safe. The specific detection and monitoring of pathological changes in the liver graft (e.g. arterial and portal vein thrombosis, or early rejection) with microdialysis should be addressed in further studies.

Presented in abstract form to the annual meeting of the International Liver Transplantation Society, Berlin, Germany, July 2001

Paper accepted 8 May 2002

British Journal of Surgery 2002, 89, 1169–1175

Introduction

After liver transplantation some degree of clinical and biochemical dysfunction occurs almost inevitably, the severity of which depends on the degree of hepatic injury[1]. Vascular and biliary complications related to ischaemia–reperfusion injury remain a problem despite improvements in preservation, technical advances and surgical skills. Hepatic failure as a result of a malfunctioning graft is a life-threatening complication during the post-transplantation period.

Early detection of impaired graft function due to arterial or portal vein thrombosis is especially important as this may enable surgical intervention at a point when complications may still be reversible. Various techniques have been used to monitor early hepatic metabolism as well as vascular complications and liver ischaemia after the operation. Apart from bile secretion studies, none of these methods has, however, been able to monitor liver metabolism continuously.

Microdialysis provides the opportunity for simple, continuous monitoring of metabolic changes in the tissue before they are reflected in peripheral blood chemistry. The basic principle is to mimic the passive function of a capillary blood vessel by introducing a catheter with a tubular semipermeable dialysis membrane on its tip into the tissue. The catheter is slowly perfused with Ringer solution while equilibration takes place with the surrounding area. The sample in the microdialysis catheter reaches the same composition as surrounding extracellular fluid. The procedure has already achieved widespread application in the investigation of metabolism and ischaemia in neurosurgery[2], skeletal muscle[3], cardiovascular surgery[4], adipose tissue[5], plastic surgery[6] and metabolic diseases[7]. It has also been used to monitor liver grafts in rats[8–10].

A number of metabolites can be measured simultaneously using the same microdialysis catheter. In particular, glucose, lactate and pyruvate (reflecting carbohydrate metabolism), and glycerol (reflecting lipid breakdown through lipolysis and the breakdown of cell membranes as a result of serious ischaemia in non-adipose tissue)[11,12], have been measured. The aim of this pilot study was to establish the technique in human subjects and to characterize the course of normalization of the above-mentioned biochemical markers in the immediate postoperative period after orthotopic liver transplantation. In addition, it was anticipated that any complications would be reflected by metabolic changes in the graft.

Patients and methods

Patients

Ten consecutive patients undergoing whole-organ orthotopic liver transplantation were studied. Venovenous bypass was used during all transplant procedures. The mean age of recipients was 52 (range 30–68) years and that of donors 44 (range 19–58) years. Four of the ten patients were diagnosed with liver cirrhosis due to hepatitis C (HCV), three with familial amyloidotic polyneuropathy (FAP), two with primary sclerosing cholangitis and one with primary biliary cirrhosis. Two of the four patients with hepatitis C were transplanted with livers from patients with FAP (*domino* whole-organ transplantation). Immunosuppression was achieved with steroids and tacrolimus. The study protocol was approved by the Ethics Committee for Clinical Studies at Karolinska Institute. All patients were given detailed information about the study and gave written consent.

Microdialysis

The principle of this technique is to mimic a capillary vessel and extract molecules from the extracellular fluid without removing fluid from the tissue. The microdialysis probe has been described in detail elsewhere[5,7,13]. It is a thin, double-lumen, concentric plastic tube with a semipermeable membrane with a cut-off of 20 000 Da at the tip. Fluid is pumped through the outer tube, and flows underneath the membrane where the exchange between extracellular fluid and perfusate takes place. At the tip, the fluid flows through a small pore and into the inner tube, before it flows back and is collected in a microvial.

After the probe was inserted into the tissue, the inlet of the tubing was connected to a microinfusion pump (CMA/106 Microinjection pump; Microdialysis, Stockholm, Sweden) and perfused continuously with isotonic sterile solution T1 (containing sodium 147 mmol/l, potassium 4 mmol/l, calcium 2·3 mmol/l; osmolality 290 mmol/kg; pH 6) (Microdialysis) at a flow rate of 0·3 µl/min. The vials with collected perfusate were placed in a CMA 600 Microdialysis Analyser (Microdialysis), which analysed dialysates for glucose, pyruvate, lactate and glycerol. The microdialysis samples were measured enzymatically. The analytes were first oxidized using analyte-specific oxidases. During oxidation, hydrogen peroxide is formed, which was detected through its peroxidase-catalysed reaction. The formation of the red–violet reaction product was finally measured photometrically at 546 nm. Changes in tissue chemistry were recorded and metabolic trends estimated.

Study protocol

At the end of the operation but before abdominal closure, a plastic guider with a steel cannula was inserted into the liver. The point of introduction was the falciform ligament and the catheter was placed in segment IV in the direction of segment VIII. After removing the steel cannula, the microdialysis catheter, 0·9 mm in diameter (CMA 70; Microdialysis), was inserted. A thin secure suture was made on the cuff, to slide on the inflow and outflow tubing, and fixed to the falciform ligament. Both inner and outer tubes were led out via the middle portion of the abdominal incision. After abdominal closure and dressing, a reference CMA 60 catheter (Microdialysis) was inserted subcutaneously into the adipose tissue over the right marginal pectoral area. This was done by lifting a skinfold with one hand and pushing the microdialysis catheter resting inside a steel slit cannula introducer through a hole in the skin made by the needle. The introducer was withdrawn while the catheter was held firmly in place. This catheter was likewise secured with a thin suture. Both catheters were connected to syringes with perfusion fluid T1.

Before the patient left the operating room, syringes with perfusion solution were placed in a microinfusion pump (CMA 106; Microdialysis) and perfusion of both catheters was started. A period of 30–60 min of perfusion was considered necessary for equilibration. Microvials were changed every hour on both catheters. Sampling was continued for 3 days after operation, when the catheters were removed. Levels of glucose, lactate, pyruvate and glycerol in the liver were measured and compared with those in the subcutaneous adipose tissue.

Data are given as mean(s.e.m.).

Results

No severe complications relating to the microdialysis were observed. Despite coagulation problems in some patients, there was no major bleeding related to insertion or removal of the catheter from the liver. Removal of the catheters was not painful. In one patient, no samples were obtained from the catheter in the liver tissue, although no obvious reason could be identified. In two patients, as a result of mobilization and increased physical activity, the catheters were accidentally removed before the end of the study. During the first 24 h after transplantation, stabilization of all parameters monitored by microdialysis was observed. Mean(s.e.m.) glucose concentration in the liver decreased from 14·1(1·7) to 9·6(0·6) mmol/l, and that in the reference tissue from 13·3(1·4) to 8·9(1·4) mmol/l (*Fig. 1a*). Intrahepatic glucose concentration was higher in the liver than in the reference tissue throughout the study. On days 2 and 3 after transplantation, levels of glucose increased periodically, with an increase in the glucose concentration in the reference tissue following an increase in the liver tissue. Glucose concentrations in blood correlated closely with results observed from the catheter inserted into the liver (data not shown).

Throughout the study significantly higher levels of glycerol were observed in the reference tissue than in the liver tissue (*Fig. 1b*). Liver glycerol levels decreased rapidly within the first 16 h after reperfusion and remained stable thereafter (62·3(7·4) and 24·3(7·5) μmol/l at 7 and 17 h respectively). At the same time, glycerol in the reference tissue decreased from 426(82) to 342(62) μmol/l, and further decreased to 251(26) μmol/l during the next 24 h. At the end of monitoring, a slight increase in glycerol concentration in the reference tissue was observed.

Increased lactate levels in the liver (7·0(1·9) mmol/l) were observed, followed by a decrease to 2·7(0·3) mmol/l during the first 24 h (*Fig. 1c*). At the same time, levels of lactate in the reference tissue were decreased, from 4·9(1·7) to 2·4(0·4) mmol/l. In the early period after reperfusion, high levels of pyruvate were observed in the reference tissue, with a peak level of 436 μmol/l (*Fig. 1d*), falling to 199(23) μmol/l at 24 h and remaining stable thereafter. Levels of pyruvate in the liver remained high (343(105) μmol/l) for the first 6 h and then decreased gradually until 24 h (238(22) μmol/l), after which there was stabilization. A decrease in, and stabilization of, the lactate : pyruvate ratio in the liver was observed, from 18·7(4·2) to 10·0(1·1), within 24 h after transplantation (*Fig. 1e*). The lactate : pyruvate ratio in the reference tissue remained stable during the entire postoperative period, at a mean level of 9·5. On day 3 after the transplantation, a slight increase in the lactate : pyruvate ratio was observed in the reference tissue.

Two cases were of particular interest and are described in detail below.

Patient 1

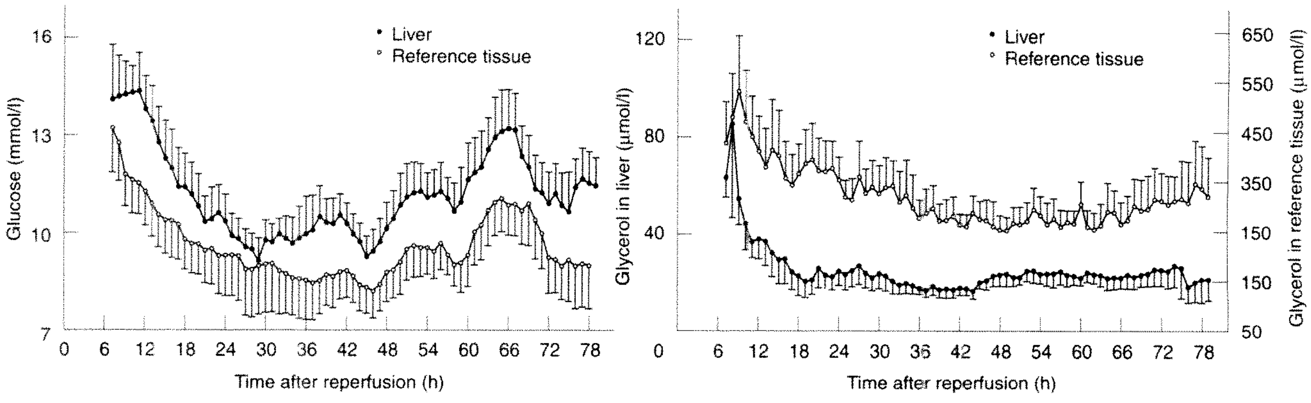
A 61-year-old man with primary sclerosing cholangitis was transplanted with a liver from a 58-year-old donor. Total ischaemia was 12 h. During the operation, portal vein flow was suboptimal. To increase portal flow, perigastric varices were ligated.

Clinically and biochemically, the liver showed no signs of ischaemia at the end of the operation and early postoperative recovery was uneventful. However, an increased level of lactate in the liver was observed on day 3. Increased lactate levels in the reference tissue and blood were observed, with a 6-h delay in comparison to lactate concentration in the liver (*Fig. 2a*). A marked increase (from 11·0 to 18·7) in the lactate : pyruvate ratio in the liver was likewise observed (*Fig. 2b*). Within 10 h after the raised lactate : pyruvate ratio, all parameters returned to previous levels. At this time, an increase in intrahepatic glycerol from 18·4 to 41·4 mmol/l was, however, measured (*Fig. 2b*). The glycerol level in reference tissue remained stable (data not shown). No other significant clinical or biochemical event was observed.

Duplex ultrasonography of the liver, performed the day before and a few days after the event observed with microdialysis, showed patent arterial and portal circulation in the liver. No conclusive diagnosis was made and monitoring with microdialysis was terminated according to the study protocol. The day after termination of microdialysis monitoring, increased levels of bilirubin and γ-glutamyltranspeptidase were observed without changes in levels of aminotransferase. At 1 week after transplantation, the patient developed clinical signs of rejection and symptoms of cholangitis confirmed by liver biopsy. Despite intensive treatment, the patient required retransplantation 4 months later.

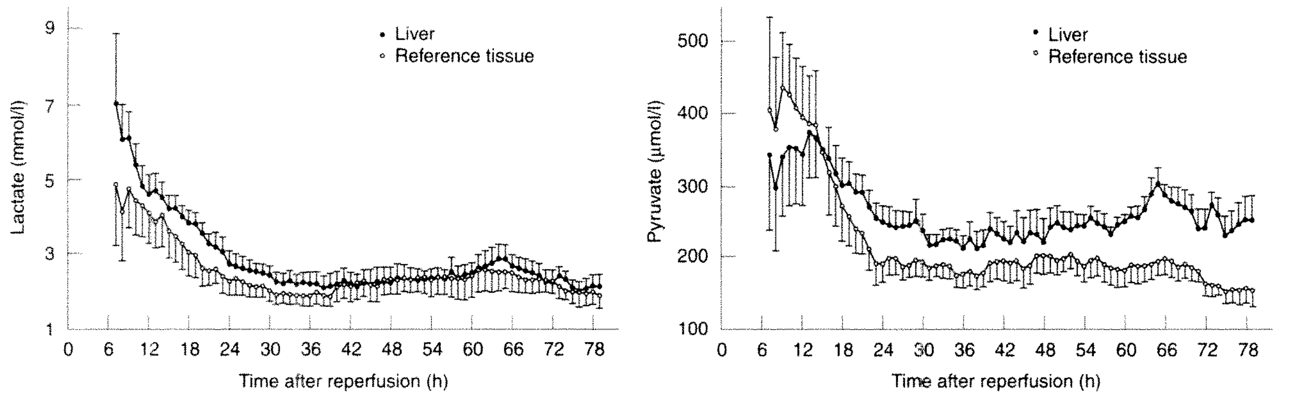
Patient 2

A 56-year-old man underwent a transplant for cirrhosis due to HCV. The liver graft was from a 67-year-old patient with FAP. Total ischaemia time was 2 h. At 18 h the patient developed thrombosis of the left iliofemoral vein where the bypass tube had been placed during the operation. At the same time, significant increases in lactate and glycerol levels



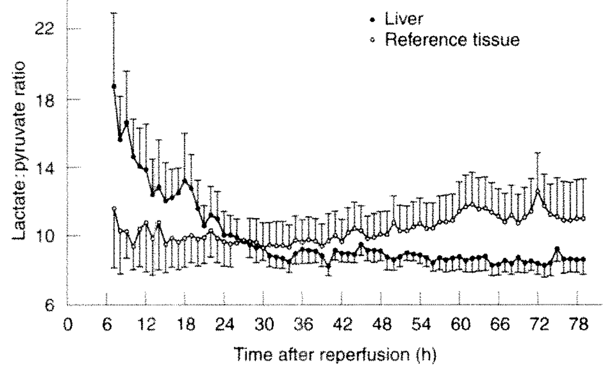
a Glucose

b Glycerol



c Lactate

d Pyruvate

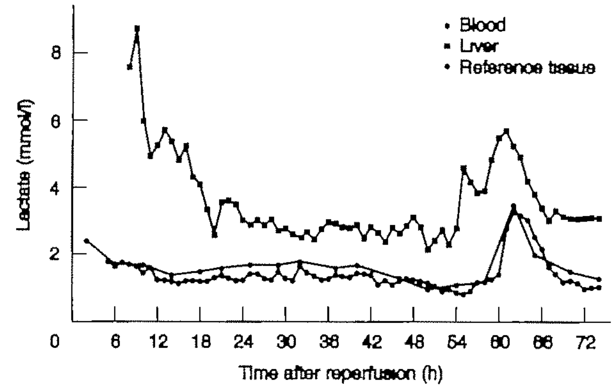


e Lactate:pyruvate ratio

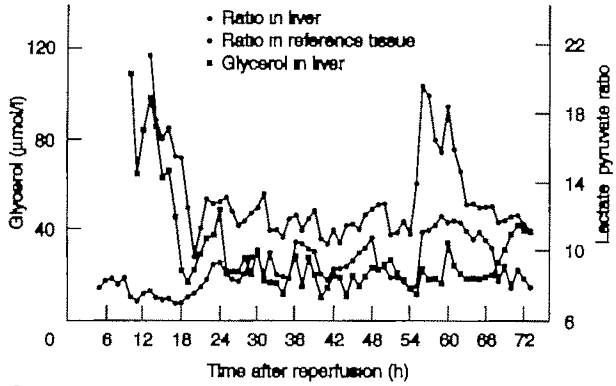
Fig. 1 Metabolic changes in liver and subcutaneous (reference) tissue monitored with microdialysis during the first 3 days after liver transplantation (data include all patients). Volumes are mean (s.e.m.). **a** Glucose – higher in liver than in reference tissue. **b** Glycerol – decreased rapidly in liver within the first 16 h after reperfusion; higher in reference tissue due to metabolism of adipose tissue. **c** Lactate – its normalization indicates recovery from ischaemia. **d** Pyruvate. **e** Lactate : pyruvate ratio – lower ratio in liver indicates recovery of liver graft from ischaemia. Stable lactate : pyruvate ratio in reference tissue, with high lactate and pyruvate levels (**c**, **d**) indicates hypermetabolic status after liver transplantation

in the reference tissue were observed (from 0·6 to 3·1 mmol/l, and from 135 to 830 mmol/l, respectively) (*Fig. 3a,b*), along with a rise in lactate : pyruvate ratio from 9·4 to 17·2 (*Fig. 3b*). The lactate level in the liver increased from 3·6 to 5·4 mmol/l (*Fig. 3a*). After successful operative thrombectomy, all parameters normalized in the liver and reference tissue.

On day 2 after transplantation, the patient developed cardiac insufficiency due to tamponade. An increased lactate level (from 1·0 to 2·2 mmol/l) was observed in the reference tissue. Lactate in the liver tissue increased from 1·0 to 1·7 mmol/l with a 3-h delay in comparison to lactate in the reference tissue (*Fig. 3a*). Increased lactate levels in the blood were observed with a 6-h delay in comparison to



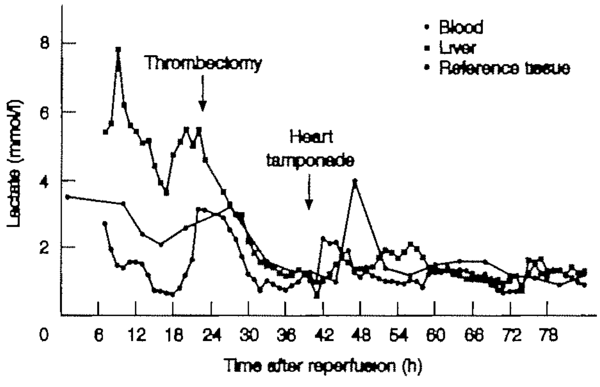
a Lactate



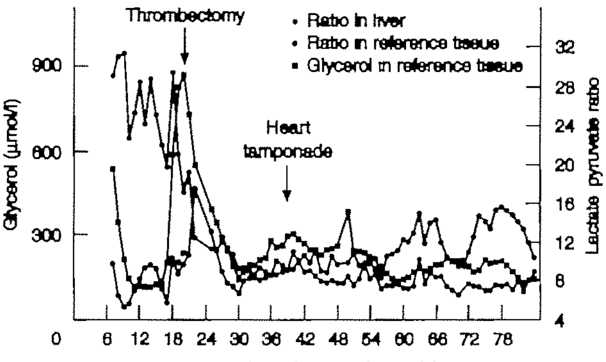
b Glycerol and lactate.pyruvate ratio

Fig. 2 a Changes in lactate concentration in liver and subcutaneous (reference) tissue monitored with microdialysis, as well as changes in lactate concentration in blood, and b changes in lactate : pyruvate ratio in liver and reference tissue, and glycerol concentration in liver, monitored with microdialysis during the first 3 days after liver transplantation in a patient with primary sclerosing cholangitis. An early increase in lactate levels in liver indicates that liver was the primary ischaemia site. The delayed increase in lactate concentration in reference tissue and blood appears to indicate a secondary change. Immediate improvement in liver function reflects decreased lactate concentration in reference tissue and blood. Increasing levels of glycerol in liver indicate cell membrane damage, followed by a short episode of ischaemia expressed by an increased lactate · pyruvate ratio

lactate in the reference tissue (*Fig. 3a*). No fluctuations in glucose, pyruvate or glycerol concentration were recorded in the liver tissue at this time. After removal of the pericardial effusion, postoperative recovery was uneventful.



a Lactate



b Glycerol and lactate·pyruvate ratio

Fig. 3 a Changes in lactate concentration in liver and subcutaneous (reference) tissue monitored with microdialysis, and changes in lactate concentration in blood, and b changes in lactate : pyruvate ratio in liver and reference tissue, and in glycerol concentration in reference tissue, monitored with microdialysis during the first 3 days after liver transplantation in a patient with hepatitis C. The patient developed deep vein thrombosis in the left leg and cardiac tamponade as a result of extensive pericardial fluid

Discussion

Although biochemical changes after orthotopic liver transplantation have been studied experimentally and clinically, there are few reports on the metabolic changes in the graft itself[14]. Hepatic artery thrombosis is a major complication in orthotopic liver transplantation, occurring in 3–12 per cent of all adult transplant recipients and in up to 42 per cent of paediatric patients[15–17]. Portal vein complications occur less commonly, with reported frequencies varying from 1 to 2 per cent[16–18]. It is sometimes difficult to detect early vascular complications in the transplanted liver solely by means of clinical assessment. Biochemical monitoring in plasma can also fail because of the dilution effect, enzymatic degradation, or binding of monitored molecules to proteins[19,20].

Early detection of impaired circulation in the transplanted liver is vital for graft survival. Various techniques are used to detect early graft failure, but none continuously measures metabolic changes inside the tissue that occur as a result of deranged liver circulation. Microdialysis should therefore be of value for surveillance purposes in transplanted livers. Metabolic changes in the tissue may be detected before they are reflected in peripheral blood chemistry, making this method attractive for monitoring transplanted organs.

One of the most important aspects of hepatic transplantation is the ability of the liver to regenerate energy-rich compounds, such as adenosine 5′-triphosphate (ATP)[21]. Failure in starting to produce energy in the liver is considered as primary graft non-function. During glycolysis, glucose is turned into pyruvate with ATP production. Pyruvate enters the citric acid cycle, provided oxygen is available. During ischaemia, lactate is produced from pyruvate in order to generate nicotinamide–adenine dinucelotide (NAD^+), which is necessary for anaerobic glycolysis. Monitoring of pyruvate concentration in the transplanted liver reflects whether energetically effective metabolism is present in the liver.

The lactate : pyruvate ratio is a well known marker of cell ischaemia, that is, of an inadequate supply of oxygen[22,23]. Cells become dependent on anaerobic glycolysis with increased production of lactate and decreased pyruvate. The lactate : pyruvate ratio increases. It is important to emphasize that lactate alone is not a good marker of ischaemia. An increase in lactate concentration may be due to hypoxia, ischaemia or hypermetabolism. While high cellular ATP levels in the stored organ correlate with favourable functional recovery after transplantation[24], depleted ATP concentration is not a reliable predictive indicator of non-viability[25]. Lactate levels and the lactate : pyruvate ratio indicate the extent of glycolysis and anaerobic metabolism in the tissue[22]. The lactate : pyruvate ratio reflects tissue reaction to changing oxygen and glucose supply.

Glycerol is an integral component of the cell membrane and can be used as a marker of cell damage[11,26,27]. Loss of energy leads to an influx of calcium and activation of phospholipases, which splits glycerol from the phospholipids in the cell membrane. The finding in one of the present patients (patient 1) supports the theory that transient ischaemia in the liver is followed by increasing glycerol levels, although metabolic changes resulting from rejection or infection could also have been responsible.

It is known from previous studies that the glucose level is affected by changes in the glucose supply from capillaries and glucose uptake into tissue[28]. In general, glucose concentration indicates the glucose available in the tissue as a consequence of plasma concentration and local blood flow in the ischaemic tissue. However, the relative impacts of glycogenolysis and gluconeogenesis merit further investigation.

The metabolic profiles described with microdialysis probably reflect a recovery of the liver graft from ischaemia–reperfusion injury. Changes observed in patient 1 indicate that these can be identified several hours before biochemical changes in blood or the onset of clinical symptoms. The procedure is easy to perform and safe. It is assumed that it can also be used to study children and other groups of patients, such as elderly and critically ill patients, without risk or discomfort. There is no need for any restriction in patient mobilization as a result of monitoring with microdialysis, and accidental removal of catheters can probably be avoided by careful fixation of the microdialysis pumps to a dressing on the abdominal wall. The specific detection and monitoring of pathological changes (e.g. arterial and portal vein thrombosis, or early graft rejection) with microdialysis should be addressed in further studies.

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Original article

Identifying patients for blood conservation strategies

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Background: Generally, only the type of operation is used to estimate the need for perioperative homologous blood transfusion. This study quantified the extent to which the estimation could be improved if, in addition, simple patient characteristics were taken into account.

Methods: Retrospective data on 24 509 consecutive adult surgical patients were used to derive and validate three models to predict perioperative homologous transfusion. The first model was a univariable model with type of operation as the only predictor. The second and third models were a full and a simplified multivariable logistic regression model. The performance of the multivariable models was tested in two validation sets: in similar patients who had operations in the same general hospital (internal validation) and in patients who had operations in a university hospital (external validation). The areas under the receiver–operator characteristic (ROC) curve were compared with that found in the derivation set.

Results: There were no important differences in characteristics between the derivation and validation sets. The ROC area of the model including surgery only was 0·92 (99 per cent confidence interval (c.i.) 0·91 to 0·94) and that of the full and simplified multivariable models 0·95 (99 per cent c.i. 0·94 to 0·96) and 0·94 (99 per cent c.i. 0·93 to 0·95) respectively. The latter two were significantly different from the first one. In the external validation set the ROC area of the simplified model was 0·84 (95 per cent c.i. 0·83 to 0·86). Patients who had a preoperative haemoglobin level lower than 13 g/dl and underwent major invasive surgery had the highest risk (43 per cent) of transfusion.

Conclusion: A simple algorithm using type of operation and haemoglobin concentration was effective in identifying patients likely to need perioperative homologous blood transfusion.

Paper accepted 1 May 2002

British Journal of Surgery 2002, **89**, 1176–1182

Introduction

Blood transfusion during operation can be life saving. Hospital procedures, such as 'group and screen' or storage of patient-specific red cell units, are aimed at the prompt availability of blood if required[1]. Homologous blood transfusion is minimized by preoperative erythropoietin administration or by blood conservation techniques, such as preoperative autologous blood donation[2–6]. These procedures are time consuming and expensive, and some may potentially harm the patient[7–9]. Meanwhile, only a minority of the patients will require a transfusion.

In most hospitals only the type of surgical procedure is used to regulate the indications for a group and screen procedure or blood conservation. Other predictors for perioperative blood transfusion such as sex, preoperative haemoglobin concentration, age and the need for emergency operation are generally not taken into account[3,10–13]. More accurate estimates of the transfusion risk in individual patients could help to restrict erythropoietin administration or conservation procedures to patients with a high-risk profile only.

The aim of the present study was to quantify the extent to which the estimation of the need for perioperative homologous blood transfusion is improved if simple patient characteristics such as age, sex and haemoglobin concentration are taken into account, in addition to the type of operation. Prediction models were derived and validated, and their generalizability was tested in patients from another hospital.

Patients and methods

Patients

The first part of the study was performed in a 638-bed non-university hospital in the Netherlands, in which neurosurgery and cardiac surgery were not performed. Data on all 9033 adult patients (aged 18 years or more) who had surgery under general or regional anaesthesia in 1998 were entered into the derivation database. This database was used to develop a model to predict the need for perioperative transfusion. Data on 6494 patients undergoing surgery between 1 January and 1 October 1999 were used to validate the applicability of this prediction model (internal validation set). To evaluate the generalizability of the model, it was subsequently applied to 8982 similar patients who had surgery in 1998 in a 1080-bed Dutch university hospital (external validation set).

Predictors

Type of surgical procedure, age, sex, emergency surgery, preoperative autologous blood donation and preoperative haemoglobin concentration were evaluated as potential predictors for transfusion outcome. Age and haemoglobin concentration were initially analysed as continuous variables, but were also included as categorized variables. Age was coded in four categories (18–29, 30–49, 50–69, and 70 years or more) and haemoglobin concentration in eight categories (less than 8, 8–9·9, 10–10·9, 11–12·9, 13–14·4, 14·5–15·9, 16 g/dl or more, and missing haemoglobin level), in which the lowest age category and the highest haemoglobin concentration category were used as reference categories. Surgical procedures were put into 14 categories with increasing transfusion incidence (*Table 1*).

Outcome

The outcome was the incidence of red cell blood transfusion on the day of operation or during the first postoperative day. Transfusion of plasma or platelets was not included. The decision to transfuse was made by the individual clinician; a protocol stating specific transfusion triggers was not in use. Generally, in transfused patients, the last haemoglobin concentration measured before transfusion was 9–10 g/dl in the general hospital and less than 8 g/dl in the university hospital. During the study, the transfusion protocol did not change in either hospital.

Data collection

After approval by the hospital ethics committee, data were retrieved from three independent databases: operation theatre, laboratory and blood bank. The unique hospital identification code assigned to each patient was used to merge these data. In case of a reoperation on the same day or the first postoperative day, only the first procedure was counted. There were no missing data, except for the haemoglobin concentration, which was not determined in 310 (3 per cent), 83 (1 per cent) and 2433 (27 per cent) patients in the derivation, internal and external validation sets respectively. Especially in the external validation set, these missing data could not be ignored. Simply excluding many subjects with missing values from the analyses (so-called complete case analyses) affects the statistical power and biases the results, because the occurrence of missing data is seldom random[14–17]. Recording missing values reduces bias and increases statistical efficiency[14–17]. Accordingly, when analysing the haemoglobin level as a categorized variable, the missing haemoglobin level was recorded as if it was in the highest category (haemoglobin level greater than 13 g/dl). This was done because, in the

Table 1 Categorization of surgical procedures according to increasing incidence of transfusion

1	Non-invasive surgery (e.g. eye or ear surgery)
2	Mildly invasive surgery (e.g. laparoscopic surgery)
3	Caesarean section and medium gynaecological surgery (e.g. vaginal hysterectomy)
4	Pulmonary surgery (e.g. lobectomy)
5	Laparotomy and small bowel resection
6	Major vascular surgery (e.g. femoral bypass)
7	Major bone surgery (e.g. hip or knee prosthesis)
8	Colonic surgery
9	Major obstetric, gynaecological and urological surgery (e.g. radical hysterectomy or radical prostatectomy with lymph node dissection)
10	Resection of the rectum
11	Hip prosthesis replacement
12	Abdominal aortic prosthesis (elective)
13	Abdominal aortic prosthesis (ruptured)
14	Oesophageal surgery

external validation set, the preoperative haemoglobin concentration was determined only if considered reasonable with respect to the expected transfusion risk (the majority of these patients underwent non-invasive surgery). Therefore, patients with a missing haemoglobin level were considered to have a normal haemoglobin level. This method was used to mimic as closely as possible future clinical practice in which the prediction rule might be applied.

Statistical analysis

The Statistical Package for the Social Sciences (release 10·1; SPSS, Chicago, Illinois, USA) was used for statistical analysis. In the derivation set, the incidence of transfusion was estimated for each surgical category and a logistic regression model to predict transfusion occurrence was fitted, using type of surgical procedure as the only predictor (univariable prediction model). In this, surgery was included as 13 indicator variables with mild invasive surgery as the reference category. The area under the receiver–operator characteristic (ROC) curve with 99 per cent confidence intervals (c.i.) was estimated to evaluate the ability of the model to discriminate between patients with, and those without, transfusion[14,18,19]. A ROC curve, in which the sensitivity (true positives) and 1 – specificity (false positives) of several cut-off points of a model are plotted against each other, reflects the overall value of a model. The area under the ROC curve can range from 0·5 (useless model, like tossing a coin) to 1·0 (perfect discrimination). A value over 0·7 can be interpreted as reasonable or fair, and over 0·8 as good[14,20]. Subsequently, the added value of all five other potential predictors was quantified using multivariable logistic regression modelling (full model), analysing age and haemoglobin level both continuously and as categorized variables. Finally, to enhance applicability, a simplified multivariable model was tested, including surgery and haemoglobin level only. In this, 'non-invasive surgery' (67 per cent of all patients) was included as in the full model; 'mild invasive surgery' (19 per cent) was the reference category and included surgical categories with a transfusion incidence of up to 20 per cent (mild invasive surgery, caesarean section and medium gynaecological); and 'major invasive surgery' (14 per cent) included the remainder of the categories. Preoperative haemoglobin concentration was included as unavailable or 'normal' (greater than 13 g/dl – reference category), as 'mild anaemia' (10–13 g/dl) or as 'severe anaemia' (less than 10 g/dl). It was determined whether this model was as predictive as the full model. To quantify the difference in discriminative ability between the univariable model and the two multivariable models, the difference between ROC areas (with 99 per cent c.i. of the difference) was estimated, taking into account the correlation between the models as they were based on the same patients[19]. The reliability (calibration, or goodness of fit) of all three models was quantified using the Hosmer–Lemeshow test[21]. This test compares the observed and predicted probabilities; a high P value (greater than 0·2) indicates that there is no difference between the probabilities (good model fit).

It is a proper methodological standard to validate the applicability of a prediction model and to evaluate its generalizability in new, but plausibly related, patients from another hospital before implementing the model in clinical practice[14,22]. Therefore, the performance of both multivariable models was tested in the internal and external validation set, estimating the calibration and the ROC area in each validation set. As a ROC area reflects the overall added value of a model and does not directly indicate its clinical value, in both validation sets the absolute number of transfused patients was estimated across various patient subgroups defined by the predictors in the simplified model[23,24].

Results

Table 2 gives general characteristics of the patients included in the study; important differences between the derivation and internal validation sets were not observed. The number of patients who received a transfusion was 651 (7 per cent) and 486 (7 per cent) respectively. The external validation set was comparable to the other two data sets, with an overall transfusion risk of 6 per cent, but including more patients having mild and major invasive surgery (risk of transfusion 2–20 per cent and more than 20 per cent respectively).

In the derivation set, the transfusion risk ranged from 0 per cent (non-invasive surgery) to 100 per cent (oesophageal surgery) in the different surgical categories (*Table 3*). The prediction model including these surgical categories yielded a ROC area of 0·92 (99 per cent c.i. 0·91 to 0·94). Adding the five other predictors to this model significantly increased the ROC area to 0·95 (99 per cent c.i. 0·94 to 0·96), a difference of 0·03 (99 per cent c.i. 0·02 to 0·04). Including age and haemoglobin level as categorical variables yielded a similar ROC area. In this model, each predictor was independently associated ($P < 0·05$) with the outcome, except for the age categories of less than 70 years and the haemoglobin categories of 14·5 g/dl and above (data not shown). Hence, age was further categorized as less than 70 years and as 70 years or more, and the haemoglobin categories above 13 g/dl were considered as one variable. The ROC area of this full model remained as 0·95; values for the regression coefficients of each variable included are

Table 2 Data on patients, surgery and red blood cell transfusion in the study

	Derivation set (*n* = 9033)	Internal validation set (*n* = 6494)	External validation set (*n* = 8982)
Mean age (years)	52	51	50
Age > 70 years (%)	23	21	17
Male sex (%)	42	42	46
Emergency surgery (%)	18	19	20
Type of operation (%)			
Non-invasive	67	67	53
Mild invasive	19	19	25
Major invasive	14	14	22
Mean preop. haemoglobin (g/dl)	13·8	13·9	13·4
Preop. haemoglobin (%)			
< 10 g/dl	3	2	3
10–13 g/dl	22	19	24
> 13 g/dl	72	78	46
Not determined	3	1	27*
Transfused patients (%)	7	7	6
Mean no. of units transfused per patient	3·4	3·5	4·2

*In the university hospital, haemoglobin concentration was determined only if considered reasonable with respect to expected transfusion risk

Table 3 Risk of transfusion per surgical category (derivation set)

Surgical category	No. of patients	No. transfused	Risk (%)
Non-invasive surgery	6053	11	0
Mild invasive surgery	1424	98	7
Caesarean section/gynaecology (medium)	331	62	19
Pulmonary surgery	59	16	27
Major vascular surgery	64	20	31
Major bone surgery	544	173	32
Laparotomy or small bowel resection	107	41	38
Colonic surgery	104	39	38
Resection of rectum	43	20	47
Obstetrics, gynaecology, urology (major)	201	95	47
Hip prosthesis replacement	32	20	62
Abdominal aortic prosthesis (elective)	37	24	65
Abdominal aortic prosthesis (ruptured)	20	18	90
Oesophageal surgery	14	14	100

Table 4 Simplified prediction model including type of operation and preoperative haemoglobin concentration only

Predictor	Regression coefficient	Odds ratio
Operation		
Non-invasive	− 3·56	0·03 (0·02, 0·05)
Mild invasive	Reference	Reference
Major invasive	1·80	6·6 (5·3, 8·2)
Haemoglobin concentration (g/dl)		
< 10	2·89	18 (13–35)
10–13	1·22	3·4 (2·7–4·2)
> 13	Reference	Reference
Intercept (constant)	− 3·13	

Values in parentheses are 95 per cent confidence intervals. Non-invasive surgery, risk of transfusion less than 2 per cent; mild invasive surgery, risk of transfusion 2–20 per cent; major invasive surgery, risk of transfusion greater than 20 per cent

available from the authors. Mild invasive surgery, age less than 70 years and haemoglobin concentration greater than 13 g/dl were used as reference categories.

The regression coefficients and odds ratios of the variables included in the simplified model are shown in *Table 4*. The ROC area of this model was slightly lower than that of the full model: 0·94 (99 per cent c.i. 0·93 to 0·95). The difference in ROC area between the simplified and full model was 0·01 (99 per cent c.i. 0·00 to 0·02). Therefore, it was concluded that the simplified model predicted transfusion requirement as well as the full model.

The estimated risks for transfusion of all three models were comparable to the observed risks, which indicated good calibration (goodness of fit). The Hosmer–Lemeshow test was far from significant, with *P* values greater than 0·3.

As the multivariable models were significantly better than the univariable model, both were applied to the two validation sets. In each validation set, for both models, the estimated risk of transfusion was comparable to the observed risk, which indicated good calibration. The ROC area of the full model was 0·89 (95 per cent c.i. 0·87 to 0·90) and 0·76 (0·73 to 0·78) in the internal and external

Table 5 Observed number of transfused patients and total number of patients across the nine categories of the simplified prediction model, applied to both validation sets

	Haemoglobin concentration (g/dl)		
	< 10	10–13	> 13
Internal validation set			
No. of patients	135	1409	4950
Non-invasive surgery (n = 4325)	13 of 48 (27)	16 of 702 (2)	12 of 3575 (0)
Mild invasive surgery (n = 1243)	10 of 18 (56)	45 of 385 (12)	37 of 840 (4)
Major invasive surgery (n = 926)	53 of 69 (77)	160 of 322 (50)	140 of 535 (26)
External validation set			
No. of patients	284	2181	6517
Non-invasive surgery (n = 4776)	6 of 70 (9)	7 of 829 (1)	10 of 3877 (0)
Mild invasive surgery (n = 2272)	9 of 111 (8)	46 of 763 (6)	73 of 1398 (5)
Major invasive surgery (n = 1934)	44 of 103 (43)	140 of 589 (24)	176 of 1242 (14)

Non-invasive surgery, risk of transfusion less than 2 per cent; mild invasive surgery, risk of transfusion 2–20 per cent; major invasive surgery, risk of transfusion greater than 20 per cent

validation sets respectively. The ROC area of the respective simplified models was 0·89 (0·88 to 0·91) and 0·84 (0·83 to 0·86).

Table 5 shows the absolute risks of transfusion for the nine possible categories of the simplified model. Patients undergoing mild invasive surgery who had a preoperative haemoglobin concentration of less than 10 g/dl, and patients undergoing major invasive surgery who had a haemoglobin concentration lower than 13 g/dl, had the highest risk of transfusion.

Discussion

These results indicate that prediction of the need for perioperative homologous blood transfusion improves if easy obtainable parameters such as age, sex and preoperative haemoglobin concentration are taken into account, in addition to the type of operation. Use of the full logistic regression model would enhance the use of blood conservation strategies before operation for individual patients, but to predict this transfusion risk a computer calculation is necessary. Although this can easily be done using a spreadsheet algorithm while planning the operation schedule, it may limit the clinical applicability. Therefore, a simplified, easily applicable, model was derived yielding similar predictive performance.

No specific transfusion trigger was used in the outcome definition because this study was pragmatic and aimed to reflect daily practice as closely as possible. Therefore, transfusion on the day of operation and the first postoperative day was chosen as the main outcome parameter to monitor the care process of both the anaesthetist (day of operation) and the surgeon (first postoperative day).

A postoperative haemoglobin concentration of less than 8 g/dl is commonly considered safe[25–27]. The last measured haemoglobin concentration before transfusion in the general hospital was 9–10 g/dl, which suggests that excessive transfusion occurred in a number of patients. In the university hospital more invasive procedures were done with a slightly lower incidence of blood transfusion. This did not affect the generalizability of the simplified prediction model, as the predictive performance of this model in the external validation set was comparable to that in the derivation set.

The aim of validating a clinical prediction model is to quantify whether the rule has good predictive accuracy in patients other than those on whom the model was fitted (derivation set). A model will always perform better in the derivation set than in a new patient sample (validation set).The ROC area found in the derivation set will be 'overfitted'[14,16,22]. Although it is anticipated that the predictive accuracy in validation sets will be lower, it should not be much lower. The question to what extent the predictive accuracy found in the derivation set is overfitted requires a validation study in a new, independent, patient population[14,16,22]. The ROC area of the full model in the external validation set (0·76) was much lower than that in the internal validation set (0·89), indicating that there was overfitting of the full model which could be the result of the large number of surgical categories. However, there was less evidence of overfitting for the simplified model.

Finally, the missing haemoglobin values were recorded as normal values. These patients did not have a haemoglobin measurement because of their low expected transfusion risk (they were scheduled for non-invasive surgery and/or had a high expected haemoglobin level). This might have caused some misclassification with regard to the true haemoglobin level of these patients, but a normal haemoglobin level was the most logical value to record. There are more sophisticated, computational methods for scoring missing values[14–17], but these will not be applicable to a practising physician. Nevertheless, the analyses were repeated after excluding the records with a missing haemoglobin level in the external validation set; this yielded a similar ROC area.

Previous studies have suggested that the predictors found in this study could be used to improve transfusion planning in patients undergoing orthopaedic, rectal and cardiac surgery[3,12,28]. Similar statistical techniques and predictors were used to derive this model, and the present study has demonstrated that these predictors are also suitable to predict the need for transfusion in a wider range of surgical procedures.

For a decade, blood-saving strategies such as preoperative autologous blood donation have been offered to patients to reduce the risk of human immunodeficiency virus infection or hepatitis. Currently, these risks are very low, but allogeneic transfusion has been reported to be associated with postoperative infectious complications and tumour recurrence after cancer surgery[28,29]. Therefore, potential benefits of blood-saving strategies should be weighed against disadvantages such as unnecessary donation, reduced preoperative haematocrit with increased risk of ischaemia and costs. It has been stated that preoperative autologous blood donation should be performed only if the risk of transfusion is more than 50 per cent[30]. In the internal validation set (general hospital), patients who had mild invasive surgery with a haemoglobin concentration of less than 10 g/dl, or major invasive surgery with a haemoglobin concentration below 13 g/dl, were at high risk (50 per cent or greater) for transfusion and would be potential candidates for blood conservation (*Table 5*). As a result of the more restrictive transfusion policy in the university hospital (external validation set), none of the nine categories in the simplified model (*Table 5*) showed a transfusion incidence greater than 50 per cent. Using this simplified model in a hospital with modern transfusion triggers, none of the nine patient categories from *Table 5* seemed to benefit from preoperative autologous blood conservation.

An algorithm that could be used in a spreadsheet computer program or at the bedside in a simplified form was effective at identifying patients likely to need homologous red cell blood transfusion over a wide range of surgical procedures. It could be used to improve the accuracy of labelling eligible candidates for preoperative autologous blood donation or erythropoietin administration.

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Assessment of the physical properties of endoscopic retrieval systems

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Background: A reliable method of retrieval of laparoscopically resected organs is required. The physical properties of three commercial systems available for clinical use (two plastic, one woven fabric) were examined.

Methods: Pig abdominal walls and gallbladders containing steel balls to represent gallstones were used to simulate organ retrieval on 60 occasions. The performance of retrieval bags was measured in terms of the temporal profile of pressure developed inside the bag, the force on the bag during withdrawal, and whether or not the bag could be retrieved intact. The force *versus* elongation relationship was also determined for each bag.

Results: Although there was a wide range of maximum pressures recorded (14–320 mmHg) with each retrieval system, the mean pressures in the plastic systems were significantly higher. The forces recorded during attempted withdrawal of both plastic bags were significantly lower than those with the fabric system (BERT bag: mean (range) 87 (25–165) N; Endocatch: 40 (7–123) N; Endopouch: 40 (14–68) N; $P = 0{\cdot}005$ Endocatch *versus* BERT, $P = 0{\cdot}004$ Endopouch *versus* BERT). The BERT bags tore more easily at the site of the grasper.

Conclusion: Plastic retrieval systems were less likely to burst than fabric systems when subjected to simulated retrieval, and required less force for withdrawal. Plastic systems may therefore be associated with less tumour seeding or gallstone spillage as a consequence of bag disruption.

Paper accepted 7 May 2002

British Journal of Surgery 2002, **89**, 1183–1187

Introduction

Since the acceptance of laparoscopic cholecystectomy in the early 1990s, surgeons have attempted laparoscopic resection of many organs ranging from the appendix to the stomach and whole colon. However, retrieval of the excised organ or tissue remains one of the most difficult problems associated with laparoscopic or minimal access surgery. Various commercial retrieval systems are available to assist in whole-organ recovery. Concerns about the effectiveness of the retrieval systems include immediate spillage of bile and gallstones[1] and, more importantly, tumour cell implantation and port-site infection following the removal of tissue through laparoscopic incisions[2–4]. To overcome these concerns some companies have produced non-porous retrieval systems, which appear at first sight to be less durable than woven systems. Since there were few published data, an attempt has been made to assess the physical properties of three systems objectively.

Materials and methods

The three types of retrieval bag chosen for this investigation are in current use in the UK: the BERT bag (Vernon-Carus, Preston, UK), the Endopouch PRO II (Ethicon, Edinburgh, UK) and Endocatch (Auto Suture, United States Surgical Corporation, Norwalk, Connecticut, USA). To measure the properties and performance of the retrieval bags the clinical situation was simulated as closely as possible using pig cadaver abdominal walls and gallbladders. The fresh abdominal walls and gallbladders were stored frozen, and then thawed when required. After defrosting, the edges of the abdominal wall were sutured to the frame of an abdo-trainer with a polypropylene suture,

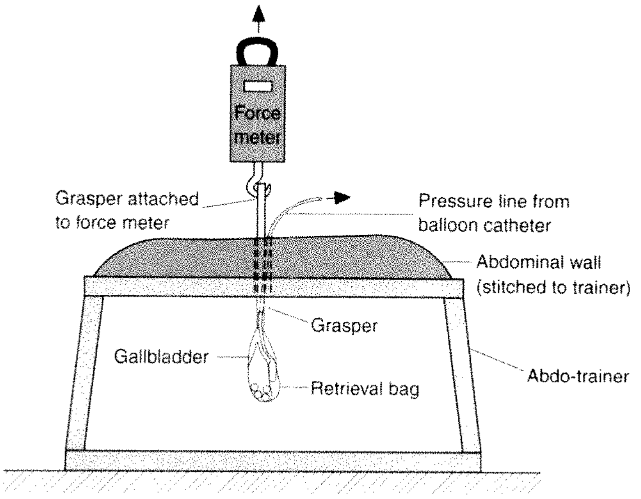

Force meter
Grasper attached to force meter
Pressure line from balloon catheter
Abdominal wall (stitched to trainer)
Grasper
Gallbladder
Retrieval bag
Abdo-trainer

Fig. 1 Experimental set-up with abdominal wall attached to an abdo-trainer, a retrieval bag containing gallbladder and stones, and a balloon catheter. A grasper inserted through a port holds the retrieval bag

and a standard 11-mm port (Ethicon) was inserted through the wall (*Fig. 1*). The gallbladders were used in four different configurations to simulate the range of possible conditions that could be encountered clinically: (1) full (bile) gallbladder with six large stones, (2) full gallbladder with six small stones, (3) empty gallbladder with six large stones and (4) empty gallbladder with six small stones.

A full gallbladder had a volume of 55 ml, approximating human capacity, and gallstones were simulated by using steel balls: 12·7 mm in diameter for large and 8 mm in diameter for small stones. Withdrawal of the gallbladders was done by a surgeon. The grasper was inserted through the port and attached to the bag, following which the port was withdrawn from the abdominal wall. The handle of the grasper was attached to a force meter. By pulling the handle of the force meter, the grasper plus bag could be withdrawn. The pressure within the bag and the force required to withdraw the bag through the port were recorded continuously during the withdrawal procedure. The pressure was recorded by placing a small air-filled balloon catheter (25 mm long, 10 mm diameter) within the retrieval bag, connected to a pressure transducer (calibrated up to 500 mmHg). The force required to withdraw the bag was recorded with a portable force meter (Mecmesin PFI200N; Mecmesin, Slinford, UK), calibrated to a maximum of 200 N. Both the force and pressure data were sampled at 0·01-s intervals for 30 s, using a data recording system designed and built by the authors. The data were then transferred to a personal computer for storage. Once the data had been collected, a spreadsheet was used for analysis and graph plotting. The total number of attempted withdrawals was 16 for the BERT bag, 28 for Endocatch and 16 for Endopouch. Bags that were not damaged during withdrawal were retested to demonstrate reproducible results.

The mechanical properties of the bags were also measured in isolation with a mechanical tensile testing machine (Instron model 1185; Instron, High Wycombe, UK). This machine enables force against elongation data to be obtained. Only two bags of each type were available for these tests, and each was tested to destruction.

Statistical analysis

The significance levels of force and pressure were calculated using the unpaired two-tailed t test. $P < 0{\cdot}05$ was considered significant. Results are given as mean (range) within the text. Standard error of the mean is also shown for each test situation in *Fig. 2*.

Results

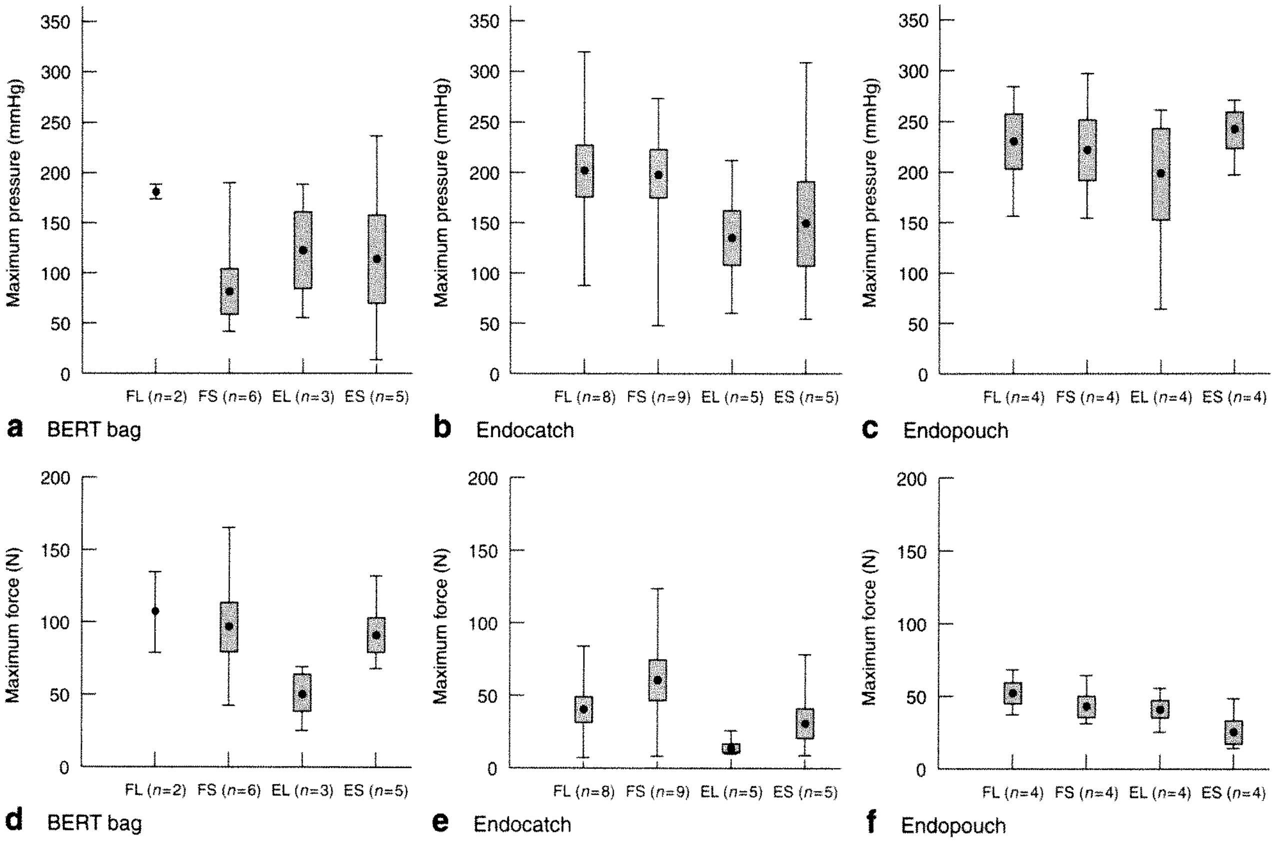
Maximum bag pressures and forces for withdrawal of the three bags are shown graphically in *Fig. 2*. *Fig. 3* shows a typical set of data demonstrating how pressure and force change during the retrieval procedure.

Effect of gallbladder loads

With a full gallbladder and six large stones, none of the bags could be pulled through the port site. The BERT bag tore, usually at the point where the grasper was holding it, and it leaked. The Endocatch and Endopouch bags did not tear, but the grasper slipped off them. Similar findings were recorded when attempting to retrieve a full gallbladder with six small stones.

The results were different with an empty gallbladder and six large stones. The Endocatch system was pulled through the port site without damage four of five times, but the Endopouch tore on all occasions. With an empty gallbladder and six small stones, the BERT bag tore five times and the grasper slipped once, but both the Endocatch and Endopouch were always retrieved intact.

Significantly less force was required to retrieve both plastic systems (BERT bag: 87 (25–165) N; Endocatch: 40 (7–123) N; Endopouch: 40 (14–68) N; $P = 0{\cdot}005$ BERT *versus* Endocatch, $P = 0{\cdot}004$ BERT *versus* Endopouch). The greatest force measured while attempting to withdraw the bags was over 150 N, approximately equivalent to lifting a 15-kg weight.



a BERT bag **b** Endocatch **c** Endopouch

d BERT bag **e** Endocatch **f** Endopouch

Fig. 2 Maximum pressure (**a–c**) and force (**d–f**) for each type of bag with different loads. Symbols, boxes and bars represent mean, s.e.m. and range respectively. FL, full gallbladder, large stones; FS, full gallbladder, small stones; EL, empty gallbladder, large stones; ES, empty gallbladder, small stones. Significantly less force was required when delivering the plastic systems

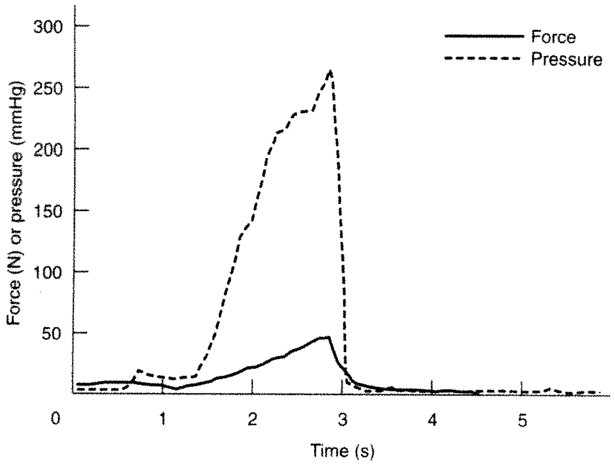


Fig. 3 Typical force and pressure exerted on a bag during a successful withdrawal procedure. The bag used was a plastic bag containing six small stones and an empty gallbladder

The pressures recorded for each system varied considerably irrespective of gallbladder load. The overall mean pressures for the plastic systems were significantly higher than those for the fabric bags (BERT: 112 (14–236) mmHg; Endocatch: 178 (48–320) mmHg; Endopouch: 222 (64–296) mmHg; $P = 0{\cdot}009$ BERT *versus* Endocatch, $P < 0{\cdot}001$ BERT *versus* Endopouch).

Intrinsic properties of retrieval systems

Measurements of tensile strength showed that the BERT bag could withstand the highest force (310 N), and was the least elongated (29 mm) (*Fig. 4*). When the BERT bag tore, smaller peaks of force were recorded as individual fibres gave way. With both tests on Endopouch bags the cords snapped before the bags tore; the bags were then tested to destruction by clamping the top of the bag within a set of jaws, similar to a surgical grasper. The graphs for the

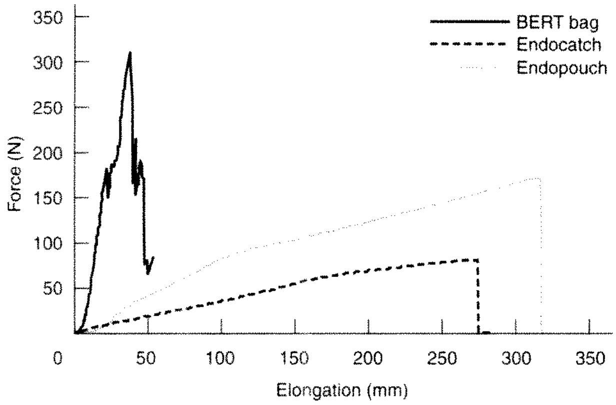


Fig. 4 Load *versus* elongation for the three types of bag

Table 1 Data from the tensile testing machine

	Maximum force (N)		Elongation (mm)	
	Individual	Mean	Individual	Mean
BERT bag		288		29
1	265		29	
2	310		29	
Endocatch		72		288
1	80		270	
2	64		305	
Endopouch				
Cord snapped		86		228
1	81		175	
2	90		280	
Hold bag in jaws		166		305
1	170		320	
2	162		290	
Endocatch cord	88		74	
Endopouch cord	72		47	

Two bags of each type were used. Data given are for the maximum load and elongation before rupture

Endocatch and Endopouch were very similar; both were much weaker than the BERT bag, but were more elastic. The results of these tests are shown in *Table 1*.

Discussion

If laparoscopic surgeons wish to use a retrieval system after resecting an organ[2], it is reasonable to expect that system to be robust. Few comparative data have been published on the physical properties of currently available systems. This study measured the intrinsic properties of three different commercial systems. The pressure exerted and force required were then measured for each bag during simulated retrieval of a gallbladder.

The tensile strength of the woven BERT bag was much greater than that of both plastic systems. As a result the BERT bag could withstand the greatest force, but this was at the expense of deformability. The plastic systems stretched to twice their resting length before breaking, whereas the fabric bag barely stretched at all. Interestingly the retrieval cord used in the Endopouch was not as strong as the bag, which could withstand twice the force exerted on the cord. It would seem appropriate to deliver the Endopouch neck using the cord and then complete organ removal by grasping the bag. The maximum intrabag pressure measurements obtained when simulating gallbladder retrieval demonstrated that considerable pressure might be applied during surgery. The type of material used in bag manufacture did not influence this pressure[5,6]. However, differences in shape and plasticity of the bag significantly affected the force required for retrieval. Both plastic systems could be delivered intact with less force than the fabric bag because of their ability to mould around the gallbladder and its contents. This was best demonstrated when retrieving an empty gallbladder containing small stones. Both plastic systems were delivered intact with little force, while the BERT bags tore in response to a significantly greater force. It would appear from this study that plastic disposable retrieval systems perform better than fabric systems. In addition, as plastic bags are non-porous, cells from neoplastic lesions are less likely to leak so reducing the risk of tumour seeding. However, the delivery port site must be enlarged for all systems when delivering a large load, to avoid bag disruption.

There is a significant difference in cost between plastic and woven systems (£80 *versus* £5 respectively), mainly owing to the complexity of the delivery and retrieval systems used for the plastic bags. This needs to be considered in the context of the overall costs of the operation and associated risks.

Acknowledgements

The authors thank Mr M. Broadhurst and Mr E. Horsefield for assistance during the mechanical testing of the retrieval bags, the manufacturers for donating retrieval bags for this investigation, and AstraZeneca, Luton, UK for financial assistance.

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Original article

Experience in the management of conjoined twins

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Background: Conjoined twins occur in approximately one in 200 000 live births. Their management is often extremely complex and experience with large numbers is restricted to a few centres worldwide.
Methods: An analysis of 17 sets of symmetrical conjoined twins managed by a single team of surgeons over a 16-year period was undertaken.
Results: Management could be divided into three groups. Those in group 1 ($n = 5$) had non-operative management, owing to cardiac fusion or gross anatomical union, and all died. Those in group 2 ($n = 7$) underwent emergency separation, when one twin was dead or threatening the survival of the sibling or where there was a correctable life-threatening associated anomaly (four of 14 survived). Twins in group 3 ($n = 5$) underwent elective separation, allowing time for detailed preoperative investigation and planning (eight of ten survived).
Conclusion: Accurate preoperative investigation, a team approach, previous experience, and meticulous operative and postoperative management contributed to the success rate achieved in this series.

Paper accepted 7 May 2002

British Journal of Surgery 2002, **89**, 1188–1192

Introduction

The incidence of conjoined twins is estimated at one in 50 000 pregnancies but, as around 60 per cent are stillborn, the true incidence is about one in 200 000 live births. There is a female : male preponderance of 3 : 1. It is generally accepted that conjoined twins arise from a uniovular gestation that fails to undergo complete separation of the embryonic disc at the 15–17-day stage. The diagnosis of conjoined twins can be made on prenatal ultrasonography as early as 12 weeks' gestation[1]. Detailed scanning at 20 weeks will accurately define the extent of the conjoined area and will determine the anatomy of the shared organs[2]. Recently, magnetic resonance imaging (MRI) has been used prenatally to provide additional information on shared viscera[3].

Conjoined twins are classified according to the most prominent site of union plus the Greek postfix 'pagus', meaning fixed. Thoracopagus is the most common variety accounting for 40 per cent of reported cases, followed by omphalopagus (32 per cent), pygopagus (19 per cent), ischiopagus (6 per cent) and craniopagus (2 per cent). Parapagus is the term used where there is extensive 'side-to-side' fusion.

Hoyle[4] reviewed 167 attempts at surgical separation published up to 1987. The overall survival rate was 64 per cent. Thoracopagus, craniopagus and omphalopagus were associated with the highest mortality rate (51, 48 and 32 per cent respectively), while lower mortality rates occurred with ischiopagus (19 per cent) and pygopagus (23 per cent). These statistics must be viewed with circumspection as success is more likely to be reported than failure.

Patients and methods

In the 16-year period from 1985 to 2000, a single surgical team has been involved with the management of 17 sets of symmetrical conjoined twins whose management fell into three distinct categories: non-operative, emergency separation and planned separation.

Results

Group 1: non-operative management (*Table 1*)

No operative procedure was offered where there was a complex cardiac union without the possibility of reconstructing even a single functioning heart. This circumstance

Table 1 Clinical details of conjoined twins in whom no separation was attempted (group 1)

Case	Year	Type	Sex	Shared organs	Associated anomalies	Outcome
2	1986	Thoracopagus	F	Complex cardiac fusion, pericardium, liver, common bile duct, small intestine	Pulmonary atresia, oesophageal atresia and tracheo-oesophageal fistula	Both died at 3 days
4	1989	Thoracopagus	F	Complex cardiac fusion, small intestine, liver	Exomphalos, ventricular septal defect, coarctation	Both died at 4 weeks
8	1994	Thoracopagus	F	Complex cardiac fusion	No necropsy	Both died at 3 days
11	1996	Parapagus	F	Thoracoabdominoischiopagus	(Normal triplet). No necropsy	Both died at 5 days
16	1999	Thoracopagus	F	Complex cardiac fusion	Hydrops. No necropsy	Both died at 1 day

Table 2 Clinical details of conjoined twins who underwent emergency separation (group 2)

Case	Year	Type	Sex	Age at operation	Shared organs	Associated anomalies	Outcome
1	1985	Thoracopagus	F	3 days	Pericardium, diaphragm, liver, common bile duct, proximal small intestine	Pulmonary atresia	1 alive and well, 1 died at 6 weeks
6	1993	Omphalopagus	F	1 day	Liver, distal small intestine, anorectal anomaly (cloaca)	Exomphalos ruptured at birth and liver split. One dead	Both died at 1 day
10	1995	Thoracopagus	M	8 days	Cardiac (atrial communication), pericardium, liver	1 unilocular heart, 1 absent hepatic vein	1 immediate death and 1 died at 6 weeks
13	1997	Thoracopagus	F	1 day	Cardiac fusion, pericardium, liver	Diaphragmatic hernia, unilocular heart	1 immediate death and 1 died at 1 day
14	1998	Omphalopagus	F	2 days	Liver, upper small intestine	Exomphalos, volvulus of small intestine, proximal and distal intestinal atresia	Both alive and well
15	1999	Omphalopagus	M	3 h	Small intestine, bladder	Hypoplastic lungs and horseshoe kidney	1 died before operation, 1 alive and well
17	2000	Parapagus	F	1 day	Lung, diaphragm, aorta, liver, intestine	Atrioventricular canal. Persistent pulmonary hypertension	1 died at operation and 1 died after operation

pertained in four of the eight thoracopagus conjoined twins. All four died within a short period of birth. Separation was declined in one set of parapagus twins who were united extensively and where there was a normal triplet. This conjoined pair died on the fifth day of life.

Group 2: emergency separation (*Table 2*)

Emergency separation was necessary in seven sets of conjoined twins. Prenatal diagnosis failed to confirm the diagnosis in an omphalopagus set born by vaginal delivery. Following rupture of the shared exomphalos, the united liver split, causing massive blood loss and resulting in the immediate death of one twin. An emergency procedure was undertaken to salvage the surviving twin, who died at the end of the procedure. Cardiac instability prompted urgent separation on day 3 and day 8 of life, respectively, in two sets of thoracopagus twins. In the first set, one girl, currently 15 years old, survives but her twin died at 6 weeks of age from pulmonary atresia. In the second set, one twin had a unilocular heart and died at separation. The remaining twin survived the surgical procedure but succumbed to a cot death at 6 weeks of age. Emergency separation at 16 h of age was attempted but failed in a set of thoracopagus twins with a conjoined heart and an associated congenital diaphragmatic hernia. Separation was performed on omphalopagus twin girls in whom prenatal volvulus of the conjoined intestine had occurred. The affected intestine had become necrotic and perforated, while the proximal and distal small intestine sealed as atresias. Both twins survived, albeit with foreshortened intestines which required many months for adaptation to occur. The more recent set of omphalopagus twins was diagnosed at 18 weeks' gestation. They were delivered by caesarean section at 38 weeks. One twin suffered severe respiratory distress requiring mechanical ventilation. He failed to respond to intensive resuscitation and died during transfer. The conjoined area was compressed digitally and emergency separation of the

Table 3 Clinical details of conjoined twins who underwent planned separation (group 3)

Case	Year	Type	Sex	Age at operation	Shared organs	Associated anomalies	Outcome
3	1987	Ischiopagus[5]	M	8 months	Liver, distal ileum and colon, crossed ureters, genitalia	Imperforate anus	Both alive and well
5	1992	Parapagus[6]	F	3 years	Pericardium, diaphragm, liver, distal ileum and colon, bladder and vagina	Single kidneys	1 alive and well, 1 died after 3 days
7	1993	Parapagus	M	10 months	Pericardium, liver, distal small intestine and colon, crossed ureters, genitalia	Anorectal anomaly	1 alive and well, 1 died after 6 months
9	1994	Thoracopagus[7]	F	3 months	Pericardium, diaphragm, liver, bile ducts, small intestine	Exomphalos, extrahepatic biliary atresia	Both alive and well
12	1997	Omphalopagus	F	3 months	Liver	—	Both alive and well

surviving male infant was performed successfully. One set of parapagus conjoined twins had three lungs. One of the twins had a severe congenital cardiac malformation (atrioventricular canal). Shortly after birth they developed intractable severe persistent pulmonary hypertension. The condition of the twin with the cardiac anomaly was critical and was jeopardizing the survival of her sibling. One twin died during operation and the other within a few hours of separation.

The survival rate for emergency separation was four of 14 infants, but survival was not expected in four sets, including two with cardiac connections, one of the omphalopagus twins with hypoplastic lungs and the pair of parapagus twins with severe persistent pulmonary hypertension.

Group 3: planned separation (*Table 3*)

Appropriate investigations were performed to define accurately the nature and extent of shared viscera. Imaging studies carried out ranged from ultrasonography and contrast radiology to angiography, computed tomography with three-dimensional reconstruction and MRI. There were five sets of conjoined twins in this group: two parapagus and one each thoracopagus, ischiopagus and omphalopagus. The ages at separation ranged from 3 months to 3 years. One each of the parapagus twins has survived following extensive surgery involving the thorax, abdomen and pelvis. One twin died on the third postoperative day from cardiac insufficiency and the other died 6 months after separation from an aspiration event. Both twins in the ischiopagus, thoracopagus and omphalopagus sets are alive and well. The survival rate in this group was eight of ten.

Discussion

Prenatal diagnosis of conjoined twins is likely in countries where pregnant mothers are scanned routinely by ultrasonography. Inevitably, as occurred in one of the present sets, the diagnosis is missed on occasion. This is more likely to occur with lesser degrees of conjunction and may result in inappropriate attempts at vaginal delivery. Suspicion of conjoined twins therefore should prompt referral to a regional obstetric centre for more detailed imaging. In all cases, the anatomy of the hearts, livers, kidneys and bladders should be thoroughly assessed. Cerebral malformations are unusual except in craniopagus twins.

Once the diagnosis has been confirmed, the parents should receive advice on the possible outcomes of the pregnancy. This advice is best provided by the team that will be involved in any attempt at possible separation.

On the basis of the present experience, it is strongly recommended that delivery should take place within or close to the surgical unit in which the separation will take place. In addition, immediate transfer to the surgical unit should then follow. Delivery must always be by caesarean section.

Early operation is not always required but the variability of anatomy and the unpredictable behaviour of the twins mandate early assessment. In one recent set, unexpected intestinal perforation occurred before delivery. This was not immediately appreciated and transfer was delayed. Subsequently, the infants became very unstable and, although successful transfer and separation were achieved, it was felt that their course was more fraught than was necessary.

In a further instance, pulmonary hypoplasia resulted in the death of one twin within hours of delivery. Digital compression of the connecting bridge prevented exsanguination of the live baby (high-pressure circulation) into its deceased sibling. As planned delivery had occurred in close proximity, rapid transfer and separation were achieved, and the survivor remains well. It is dangerous to apply a surgical clamp to the connecting bridge under these circumstances as both sets of intestines may reside in one twin.

Initial assessment will include a complete physical examination combined with plain radiography of the chest and abdomen. On occasion, this may be all that is possible in view of the urgent need for separation. If time permits, echocardiography is useful to ascertain whether the hearts are separate. In addition, it allows the cardiologist to compare the antenatal with the postnatal appearance. Abdominal ultrasonography may be unhelpful owing to the unusual anatomy and the limited angle of examination. The main concern in omphalothoracopagus twins, aside from the cardiac anatomy, is the degree of liver union and the anatomy of the portal triads. The relevant features can rarely be distinguished.

The need for emergency separation is usually clear. Should one twin be about to succumb, immediate separation may be the only means of saving the sibling. The presence of a correctable life-threatening associated congenital anomaly (intestinal atresia, malrotation with midgut volvulus, ruptured exomphalos, anorectal agenesis) is a further indication for emergency separation.

If the twins' condition is stable and there is no indication for early separation, the authors' preference is to operate at around the age of 3 months. This allows time to carry out detailed investigations and enable separation to take place at a time when rapid expansion of the body wall can still occur to close substantial defects.

Detailed investigations will include abdominal and chest computed tomography and MRI, with particular attention to the anatomy of the hearts, livers and genitourinary systems[8]. Should the livers be joined, there will necessarily be concern about the presence of two gallbladders and two sets of hepatic veins. Although the authors have not yet encountered twins with only one portal vein, they have dealt with a twin with no hepatic veins. This twin also had a unilocular heart and died after separation. As it has not been possible to define the biliary anatomy accurately before separation, this problem has been addressed during the operation. One twin was subsequently found to have extrahepatic biliary atresia which was successfully corrected[7].

Gastrointestinal contrast studies performed to demonstrate the presence and level of conjunction have been unhelpful. Similarly, contrast angiography has been disappointing, partially as a result of being able to view the images in only one plane. Angiography has been requested only to answer a specific question about visceral blood supply. MRI angiography with three-dimensional models may provide this information.

It is also necessary to establish the urinary anatomy. In ischiopagus and pygopagus twins there is great variability in the urinary anatomy. The upper tracts are usually normal but in parapagus twins, when two bladders were present, each bladder received one ureter from each twin[9].

Once sufficient information on anatomy is available, separation is planned. In the past the authors have commenced with the use of tissue expanders when a large body-wall defect is anticipated, but these have proved troublesome and have not substantially eased reconstruction. Planning meetings are essential. These will include those involved in preoperative investigations as well as those who will participate in the separation and postoperative management. In addition, laboratory staff, psychologists, chaplains, medical illustration and the public relations department are included. Generally, one such meeting suffices shortly before the planned operation. 'Dry runs' in the operating theatre have not been used.

The operating team has consisted of the same two consultant surgeons with their surgical trainees. Two anaesthetic consultants are assisted by two anaesthetic trainees and operating theatre assistants. The team is completed with two sets of theatre nurses. Assistance has been provided by colleagues in other surgical specialties such as urology and cardiac surgery.

In planning the details of the operation, it has been found that the early steps can be undertaken as envisaged. Following induction of anaesthesia and insertion of the necessary intravascular monitoring lines, the infants are positioned on the side opposite to the preferred operative approach. The skin and deep fascia are divided to a convenient level, a swab is left in the wound and the skin is approximated with a continuous suture. The rationale for this is that there is a predetermined site to work towards in the final stages of separation. The infants are then carefully turned to the 'operative side', ensuring that all tubes and lines are securely attached. Although the subsequent stages have sometimes been planned in detail, the agreed sequence of steps has never been followed; invariably, the anatomy or the babies' conditions have dictated a change in the order of events. Therefore the initial steps are planned in detail and a flexible approach is adopted thereafter, which is dictated by the findings at surgery. Although with modern imaging techniques the gross anatomy is known before surgery, unexpected and significant problems, including biliary atresia and absent hepatic veins, have been encountered repeatedly.

It has also been noted, particularly in parapagus twins, that one infant is thinner, consumes a higher proportion of the nutrition and is more active than its sibling. The 'active' twin has a higher metabolic rate than the well nourished sibling[10]. Following separation, the 'active' twin has fewer problems with cardiovascular performance than the 'inactive' twin who experiences a period of relatively poor cardiac performance. This may be obvious during the operative procedure when a high central venous pressure (CVP) will result in visible cardiac dilatation. It has been necessary to manage these twins by reducing cardiac preload and maintaining a low CVP, accepting a somewhat reduced blood pressure. It has not been possible to detect this reduced cardiac performance by preoperative investigation and in all cases ejection fractions were normal on echocardiography. Failure to appreciate this occurrence contributed to the death of one twin.

During division of the livers, inability to distinguish which segments were joined has not proved to be a problem and the optimal line of division is usually evident. Division of the liver has been simplified by use of an ultrasonic dissector, bipolar diathermy and the use of Tisseel (Baxter Healthcare, Thetford, UK) to reduce postoperative oozing. There are no rules about assigning shared organs. The decision is made at the time of separation on the basis of what is possible and in the best interests of the infants.

Common intestine is shared equally for each infant. With a shared perineum, one twin will receive the urethra and the other the anus with urinary diversion and colostomy as reconstructions respectively. Assigning genitalia raises a problem. In the presence of a single penis, one twin will receive the male genitalia. This raises the issue of gender reassignment in the sibling. Occasionally, the phallus will have additional corpora and it may be possible to reconstruct a penis for each of the twins.

Achieving body-wall closure is a continuing problem. The preference at present is to use polypropylene mesh, securely anchored to the edges of the defect. The initial closure should be lax. Beneath this a plastic liner is placed to prevent adherence of the viscera to the mesh and to reduce fluid loss. The mesh is then plicated on a daily or alternate-day basis. With larger defects, it may not be possible to achieve complete muscle approximation and some mesh may need to remain *in situ*. At the stage of final closure, the plastic liner is removed. It is usually possible to achieve full closure within 2 weeks of separation.

After operation, in addition to attention to cardiac underperformance, the main problem has been in regard to wound leakage. The wider the area of conjunction, the greater the postoperative fluid losses. If prosthetic closure has been employed, continuous leakage of fluid will occur for many days and it is important to measure losses accurately and to replace this volume for volume with plasma on an hourly basis.

Separation is probably never mandatory. Most would, however, wish to intervene when the condition of one twin was life threatening to both. Most parents would opt for surgery when faced with the possibility of having no survivor.

At the present time, there is no prospect of survival when complex cardiac union is present. In one set the union was present only at the atrial level and separation was possible. Unfortunately, the survivor died from cot death at the age of 6 weeks.

Infants who needed to undergo urgent separation had a substantial mortality rate. Most of the deaths in this group, however, were related to underlying conditions that mandated early operation. In those who were able to grow normally for some time, in whom major associated anomalies were absent, the likelihood of success was high.

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Randomized clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure (*Br J Surg* 2002; 89: 413–17)

Letter 1

Sir

We agree with the authors' conclusions that substantially fewer headaches occur with diltiazem (DTZ) cream than with glyceryl trinitrate (GTN) ointment but are surprised that the frequency of headache in those receiving topical DTZ was over 25 per cent. In our experience of over 150 patients, topical DTZ rarely causes headaches and in the two case series quoted by Kocher *et al.* only two of 110 patients (less than 2 per cent) experienced headache. In a more recent randomized trial none of 26 patients receiving topical DTZ had headache[1]. It is difficult to explain why headaches were so frequent with DTZ cream in this paper. It is incorrect and unfair for the authors to make the comment that nitrates did not cause headaches in initial case studies as the first two published studies that used topical nitrates in anal disease reported headaches in 20 and 35 per cent of patients, respectively[2,3].

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1 Jonas M, Neal KR, Abercrombie JF, Scholefield JH. A randomized trial of oral *versus* topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44**: 1074–8.
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3 Gorfine SR. Treatment of benign anal disease with topical nitroglycerin. *Dis Colon Rectum* 1995; **38**: 453–6.

Letter 2

Sir

Although we appreciate being cited we regret repeatedly being cited incorrectly. First, we studied the effect of isosorbide dinitrate, which is, albeit an exogenous nitric oxide (NO) donor, not the same as glyceryl trinitrate (GTN). Second, although our study was among the very first to report the beneficial results of chemical treatment of chronic anal fissure, it was certainly not a randomized trial. Third, Kocher *et al.* state that headaches as a side-effect were not reported in our study. Although not stated in the abstract, it was noted in the results, as well as in the discussion, that all patients experienced mild, transient headaches during the first 2 days of treatment[1]. This is considered by most authors to be the major drawback of exogenous NO treatment. Furthermore, we do not agree with the authors' statement that surgical sphincterotomy is the treatment of choice for patients who do not improve after pharmacological internal anal sphincter relaxation within 8 weeks. This is not applicable for female patients with former vaginal delivery associated with overt or occult anal sphincter defects. In these patients prolonged treatment with, or without, fissurectomy is preferable before any attempt to further damage the internal anal sphincter is made[2].

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1 Schouten WR, Briel JW, Boerma MO, Auwerda JJ, Wilms EB, Graatsma BH. Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut* 1996; **39**: 465–9
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Authors' reply

Sir

We thank Acheson *et al.* and Briel *et al.* for their useful comments. Constraint of space precluded reporting of side-effects as unlikely, possibly, probably or definitely related to the treatment. Headaches occur in the general population at a frequency of 5–10 per cent. Only two of the eight patients who reported headache with diltiazem had this attributed as probably or definitely related to treatment. We agree that two of the other smaller series did report headaches with nitrates, but these were reported as mild or transient. In the discussion section we classified the work of Schouten *et al.* as that with nitrates, to encompass all work done with glyceryl trinitrate as well as isosorbide dinitrate. The work by Schouten *et al.* is quoted in our introduction and discussion in the context of the series and not as a randomized controlled trial. As confirmed by the authors' letter, the initial case series reported headaches to be non-significant (mild and transient). We agree that in those patients mentioned above by Briel *et al.* (who form a minority of patients seen in primary and secondary care), persistence with pharmacological treatment may be recommended. However, in the vast majority of patients with failed treatment it may be best to use the standard treatment of surgical sphincterotomy.

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Levels of the chemokines growth-related oncogene α and epithelial neutrophil-activating protein 78 are raised in patients with severe acute pancreatitis (*Br J Surg* 2002; 89: 566–72)

Sir

Approximately 25 per cent of patients with acute pancreatitis go on to develop severe disease[1]. In the present study the patient population is somewhat skewed (53 per cent had severe acute pancreatitis). This distribution introduces a bias such that it magnifies the statistical significance of findings in the severe acute pancreatitis group when compared with mild pancreatitis or with normal controls.

The authors do not mention if the statistical methods include correction for testing multiple variables, and no mention is made of a sample size justification. Finally, the quoted increase in cytokine-induced neutrophil chemoattractant expression in rat pancreatic acinar cells under caerulein stimulation is by no means uniformly seen, as a paper by the same group suggests[2].

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1 Neoptolemos JP, Raraty M, Finch M, Sutton R. Acute pancreatitis: the substantial human and financial costs. *Gut* 1998; **42:** 886–91.
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Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer (*Br J Surg* 2002; 89: 586–90)

Sir

We are concerned that prognostic factors such as grade of tumour, vascular invasion and T staging were not included in the analysis[1]. It is also not clear whether total mesorectal excision was performed for all patients with rectal cancer during this interval[2]. If only some had total mesorectal excision it may have affected the survival rate. As the authors have shown the deprived group received less adjuvant therapy than the affluent group (5 *versus* 16, $P = 0{\cdot}01$), these patients should have been excluded from the analysis since it may have affected the survival rate. We wonder whether it may have altered their results if all these factors were analysed.

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1 Kraemer M, Wiratkapun S, Seow-Choen F, Ho YH, Eu KW, Nyam D. Stratifying risk factors for follow up: a comparison of recurrent and non-recurrent colorectal cancer. *Dis Colon Rectum* 2001; **44:** 815–21.
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Ultrasonography is superior to plain radiography in the diagnosis of pneumoperitoneum (*Br J Surg* 2002; 89: 351–4)

Sir

Shen *et al.* suggest that surgery is the 'gold standard' for the diagnosis of pneumoperitoneum. Although the association between pneumoperitoneum and hollow organ perforation is obvious, the proportion of free intraperitoneal air is not always the same. There are other places free intraperitoneal air can be found, where ultrasonography is not successful. There are also pitfalls to be avoided during ultrasonography for pneumoperitoneum. Computed tomography may be required to do an exact corroboration with ultrasonography findings. There was a high prevalence of hollow organ perforation among the patients in this investigation (90·4 per cent) which gives a high pre-test probability to the study, and increases the chance of proving that ultrasonography is better for the diagnosis of pneumoperitoneum. Ultrasonography is very helpful in the diagnosis of abdominal pain, but its use in pneumoperitoneum needs further investigation. Computed tomography remains the most sensitive imaging test for the detection of free intraperitoneal air; the success rate is between 83 and 100 per cent.

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Author's reply

Sir

As pneumoperitoneum is mostly the result of hollow organ perforation, we included only patients with suspected perforation and thus the prevalence was high in the study group. Ultrasonography does not diagnose every patient with intraperitoneal free air, and we therefore pointed out some pitfalls and techniques needed to improve the examination for pneumoperitoneum. Although computed tomography is the most sensitive imaging test, its routine use is neither practical nor cost effective[1]. More than 80 per cent of the intraperitoneal free air can be detected by plain radiography and in many cases this investigation is sufficient. Ultrasonography is reserved for patients with suspected hollow organ perforation where plain radiography fails to detect the pneumoperitoneum. Computed tomography is reserved for occasions when ultrasonography still fails to make the diagnosis.

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1 Woodring JH, Heiser MJ. Detection of pneumoperitoneum on chest radiographs: comparison of upright lateral and posteroanterior projections. *AJR Am J Roentgenol* 1995; **165:** 445–7.

Erratum

M. H. Arastu, A. Chandra, A. Anggiansah, W. J. Owen. Persisting symptoms after treatment for achalasia: are clinicians diagnosing the problem? *Br J Surg* 2002; **89**(Suppl 1): 88 (Poster 35).

Please note that the last line of the table accompanying this abstract was omitted. The complete table is reproduced below. The publisher apologizes for this error.

		Pre-referral diagnosis accuracy (%)	
Patient groups	MTI (months)	Persistent achalasia	Post-treatment reflux
Group 1	56	100	40
Group 2	72	100	0
Group 3	140	100	50

Esophageal Surgery. 2nd Ed.

F. G. Pearson, J. D. Cooper, J. Deslauriers, R. J. Ginsberg, C. A. Hiebert, G. A. Patterson and H. C. Urschel (eds)

220 × 285 mm. Pp. 990. Illustrated. 2002. Edinburgh: Churchill Livingstone. £165·00.

The oesophagus, strategically secluded in the neck, posterior mediastinum and abdomen is, by its remote inaccessibility, a major challenge to surgeons. The two diseases that most frequently require oesophageal surgery (gastro-oesophageal reflux and oesophageal cancer) also test surgical techniques and decisions. *Esophageal Surgery* is a reference book written mainly by thoracic surgeons that attempts to provide established surgeons with the broadest possible surgical armamentarium for tackling oesophageal disease.

I enjoyed the trauma section including the controversies of the management of corrosive injury, oesophageal foreign bodies and perforation. Lessons in how and when to assess the extent of mucosal injury after ingestion of corrosive substances, and reminders never to miss the diagnosis of Boerhaave's syndrome 'what one knows, one sees' (Goethe), are combined with useful specialist insights. Other parts of the text reflect surgical dogma that is no longer true. Palliative oesophagectomy for cancer and bypass surgery for unresectable disease is promoted. There may be a role for this approach in Asia, but little evidence supports this view in Western countries. Information about chemotherapy and radiotherapy as adjuncts to surgery is poor, and emphasis is given to the difficulties of interpreting data from clinical trials in oncology while unsubstantiated surgical beliefs are ardently supported. The addition of algorithms for complex management pathways and a chapter summarizing complications of oesophagectomy would be helpful. Nevertheless, this wealth of thoracic surgical experience may be a useful asset to those who practise oesophageal surgery.

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The Practice of General Surgery

K. I. Bland (ed.)

285 × 225 mm. Pp. 1260. 2002. Philadelphia, Pennsylvania: WB Saunders. $139.00.

This is a substantial textbook of general surgery in a competitive market. It is aimed at surgeons in training at resident and registrar level and practising general surgeons. It is not intended to replace undergraduate or specialist textbooks. The authors are from a wide range of institutions, mostly in North America

The content covers those specialist areas which come under the broad definition of general surgery – gastrointestinal, oncology (including breast and melanoma), endocrine and vascular. It also incorporates sections on trauma and burns, head and neck and critical care, and shorter sections on paediatric surgery and gynaecology. To write a textbook which covers such a range of subspecialties at this level is an ambitious task. The sections are well laid out and the information is readily accessible. Although necessarily fairly brief, the editors have succeeded in covering this wide spectrum in considerable depth. Not only are the general principles of surgical management discussed but also, to a useful level, operative techniques. The underlying biological basis for surgical disease is also discussed in some sections.

There is a strong emphasis on gastrointestinal surgery, accounting for approximately half of the book. This perhaps defines its major target as being practising general surgeons rather than surgeons in training, who might require more balance with other subspecialties. The absence of sections on cardiothoracic and transplant surgery is somewhat incongruous in the context of sections on gynaecology and head and neck surgery, and might also reduce the utility of this book as a single volume text for trainee surgeons preparing for specialist exams.

This is a concisely written book which is structured in such a way as to be genuinely useful to experienced surgeons and of some benefit to surgeons in training.

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Urology: A Handbook for Medical Students

S. Brewster, D. Cranston, J. Noble and J. Reynard

245 × 190 mm. Pp. 153. Illustrated. 2001. Oxford: BIOS Scientific Publishers.

The teaching of urology in undergraduate medical schools has become somewhat contracted over the years and it is important that this tendency be reversed. In addition, from the urologists point of view, it is important that we continue to attract students and trainees into the subspecialty as early in their training as possible. For this reason I welcome textbooks aimed at medical students and basic surgical trainees. Although this book is quite clearly aimed at medical students it could also be relevant to senior house officers. There are already books for medical students, for example, *Essential Urology* by Bullock, Sibley and Whitaker, the second edition of which was published in 1994, and *Essentials of Urology*, edited by Corriere, published in 1986. The publication of this book is therefore timely.

It is presented in an easily accessible way. The first two chapters relate to history taking, examination, and urological investigation. Following this, all of the main topics in urology are dealt with and, generally, the quality of the illustrations is good. It is a definite plus that most chapters end with 'key points' followed by case presentations. This will help students bring what they have learned into a more meaningful clinical setting. Most chapters also include references and recommended reading. The references are satisfactory although I do not feel that many medical students would take the trouble to go directly to the literature. The recommended reading which the authors address is in most cases more complicated urological textbooks which I think are beyond the scope of the vast majority of medical students.

This is a good book for medical students to use in preparation for their final examination and would give them an interesting background to urology. The authors are to be congratulated at finding a niche between general surgical and more complicated urological textbooks. It is also suitable for pre-registration house officers and basic surgical trainees.

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Scientific Surgery

Wolterbeek JH, van Leeuwen AAM, Breslau PJ. Skin closure after infrainguinal bypass surgery: a prospective randomized study. *Eur J Vasc Endovasc Surg* 2002; **23:** 321–4.

There were no differences in the rates of superficial (8 per cent sutures *versus* 2 per cent staples) or deep (1 per cent each group) infections. Skin stapling was quicker but more expensive in this trial that included 170 patients.

Smith JJ, Brown L, Greenhalgh RM, Davies AH. Randomized trial of preoperative colour duplex marking in primary varicose vein surgery: outcome is not improved. *Eur J Vasc Endovasc Surg* 2002; **23:** 336–43.

Quality of life improved significantly after surgery in the 149 patients studied, but preoperative imaging did not improve the accuracy or outcome from surgery.

Stoiser B, Kofler J, Staudinger T, Georgopoulos A, Lugauer S, Guggenbichler JP *et al.* Contamination of central venous catheters in immunocompromised patients: a comparison between two different types of central venous catheters. *J Hosp Inf* 2002; **50:** 202–6.

Some 157 patients were enrolled; 97 were available for analysis. The use of a silver impregnated catheter reduced the rate of contamination compared with standard catheters, but the infection rates were similar (6 per cent in each group).

The EU Hernia Trialists Collaboration. Repair of groin hernia with synthetic mesh. Meta-analysis of randomized controlled trials. *Ann Surg* 2002; **235:** 322–32.

Fifty-eight studies that included 11 174 operations were reviewed. Use of synthetic mesh significantly reduced recurrence rates regardless of whether the procedure was laparoscopic or open. Persistent pain was less common after laparoscopic mesh repair.

Wright D, Paterson C, Scott N, Hair A, O'Dwyer PJ. 5-year follow-up of patients undergoing laparoscopic or open groin hernia repair. A randomized controlled trial. *Ann Surg* 2002; **235:** 333–7.

This paper reports late results of a trial that included 300 patients. Late hernia recurrence rates were similar for the two procedures.

Giovannacci L, Renggli JC, Eugster T, Stierli P, Hess P, Gurke L. Reduction of groin lymphatic complications by application of fibrin glue: preliminary results of a randomized study. *Ann Vasc Surg* 2001; **15:** 182–5.

The application of fibrin glue during closure of the groin wound after vascular surgery significantly reduced the rate of lymphatic complications.

Paulsen EK, Porter MG, Helmer SD, Linhardt PW, Kliewer ML. Thoracic epidural *versus* patient controlled analgesia in elective bowel resections. *Am J Surg* 2001; **182:** 570–7.

Pain scores were significantly lower with epidural analgesia, but return of bowel function and duration of hospital stay were similar.

Kreienberg PB, Darling RC, Chang BB, Champagne BJ, Paty PSK, Roddy SP *et al.* Early results of a prospective randomized trial of spliced vein *versus* polytetrafluoroethylene graft with a distal vein cuff for limb-threatening ischemia. *J Vasc Surg* 2002; **35:** 299–306.

The 1-year primary patency rates were similar in this pilot study of 39 procedures (44 per cent vein and 49 per cent polytetrafluoroethylene). Secondary patency was better for spliced vein but these grafts needed more frequent revision or reoperation for wound complications.

O'Hara PJ, Hertzer NR, Mascha EJ, Krajewski LP, Clair DG, Ouriel K. A prospective, randomized study of saphenous vein patching *versus* synthetic patching during carotid endarterectomy. *J Vasc Surg* 2002; **35:** 324–32.

There were no significant differences in stroke rate (3 per cent vein, 2·1 per cent synthetic patch), mortality (two patients) or complications for up to 1 year in this study that included 207 procedures. Restenosis rates were also similar.

Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabbitti P, Uomo G *et al.* Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell' Italia Meridionale. *Cancer* 2002; **94:** 902–10.

The combination regimen significantly improved the response rate and time to disease progression but median overall survival was shorter (20 *versus* 30 weeks, *P* not significant) in this study that included 107 patients.

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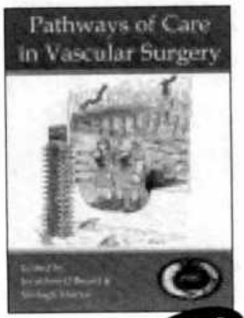

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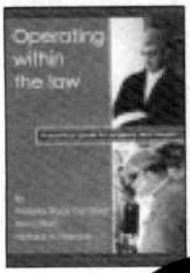

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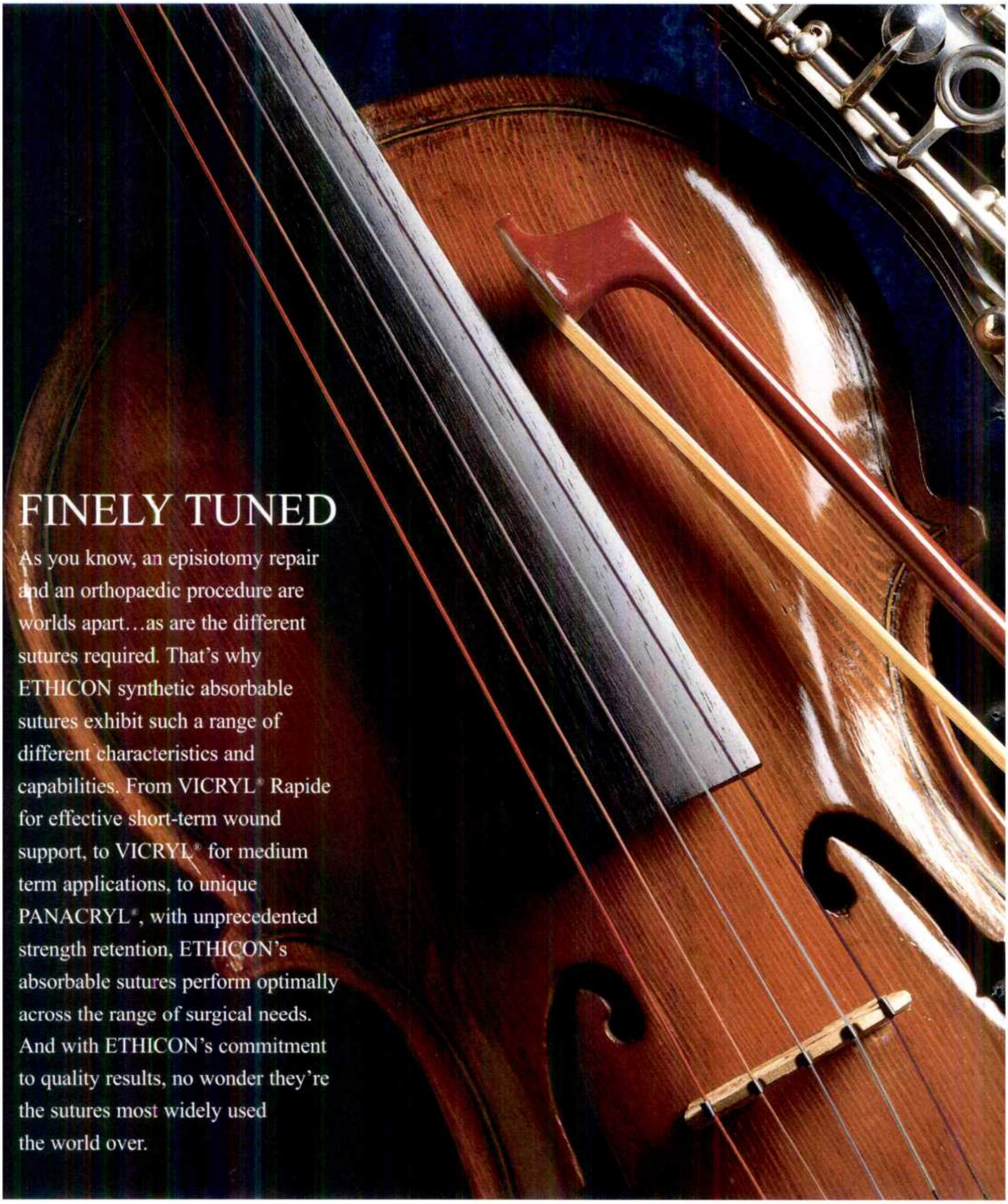

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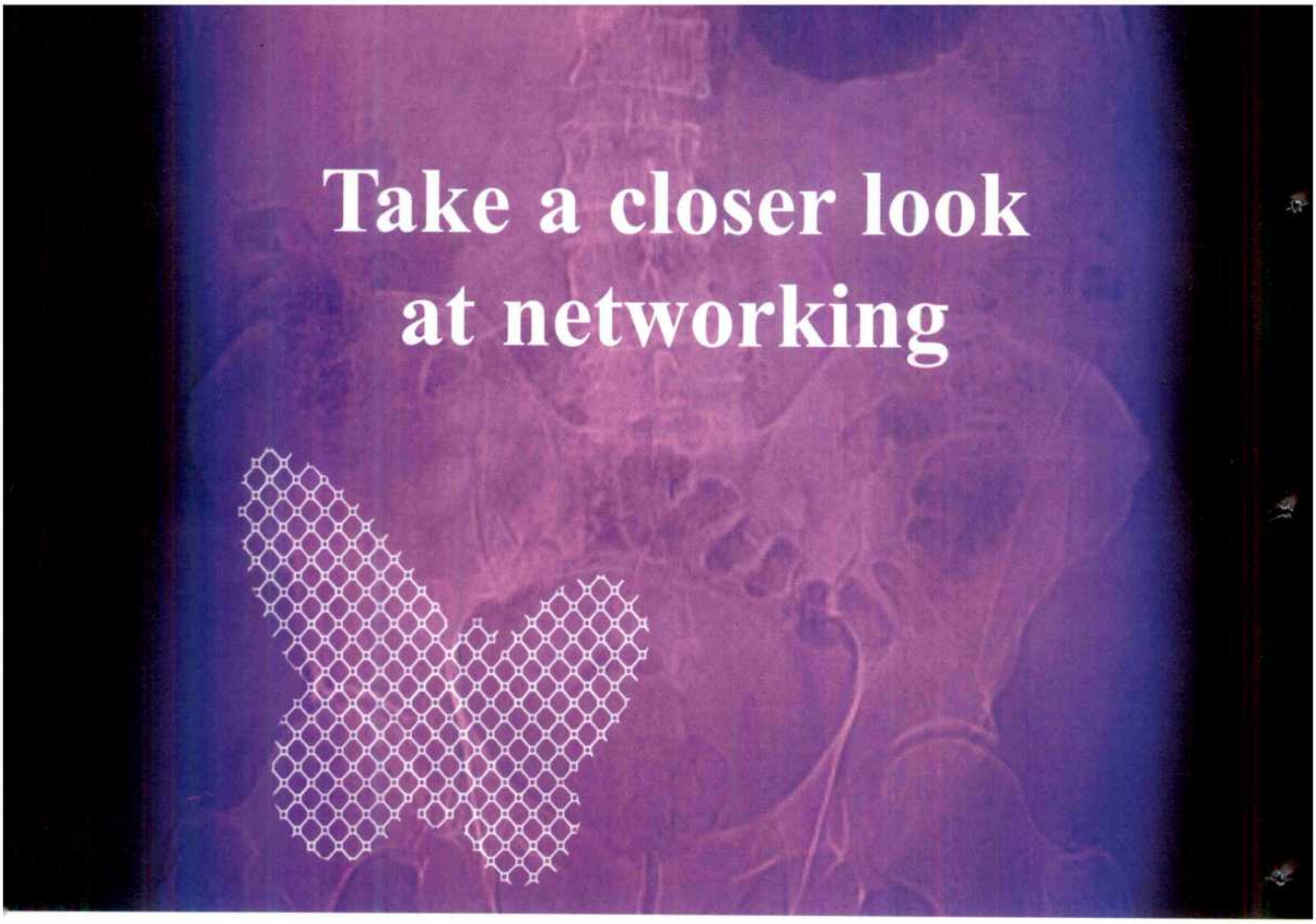

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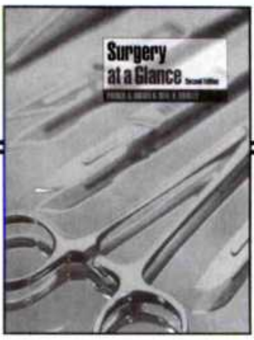

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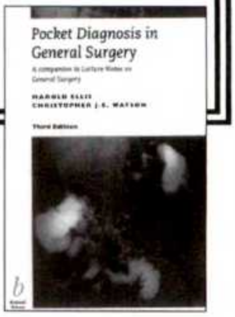

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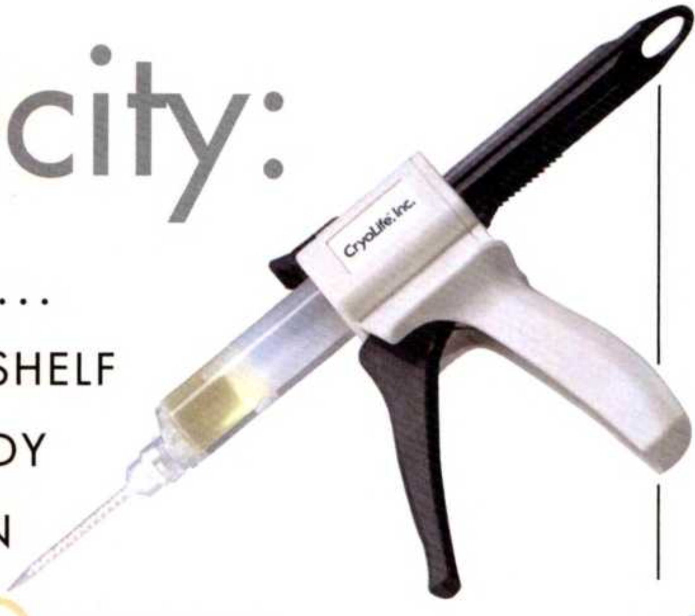

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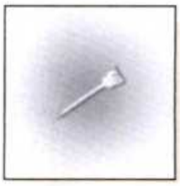

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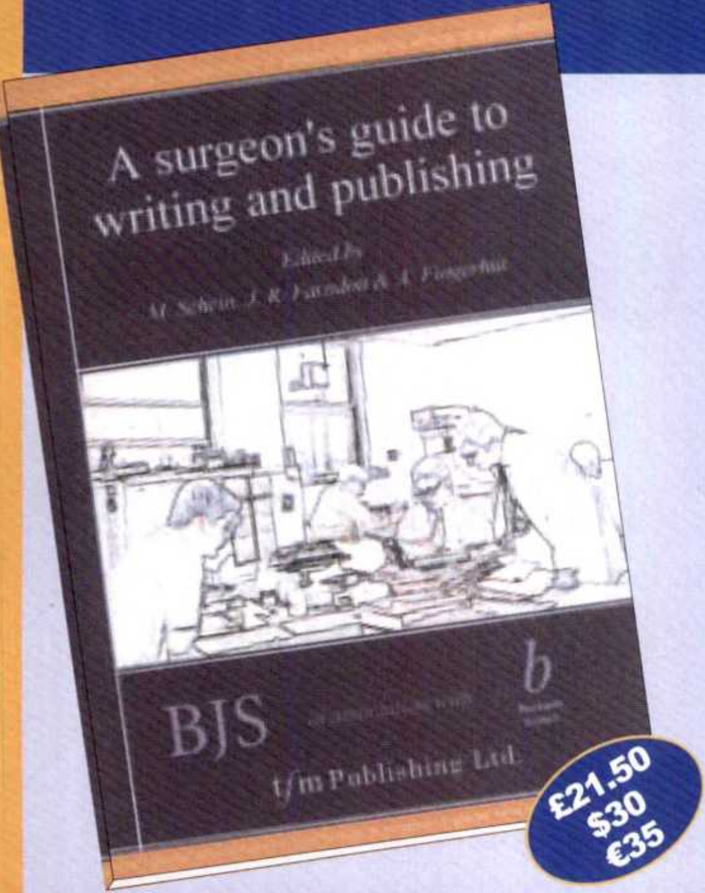
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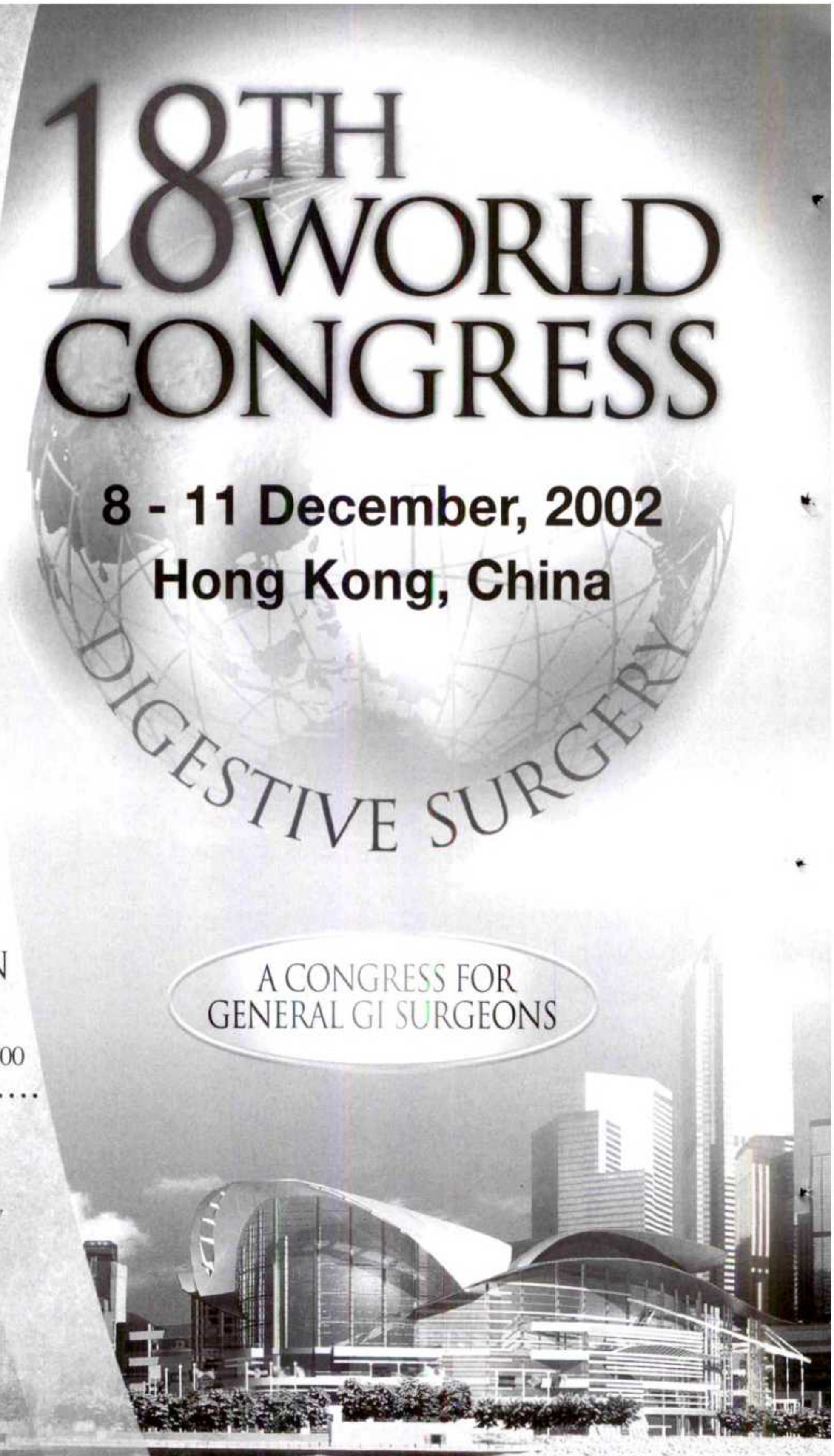

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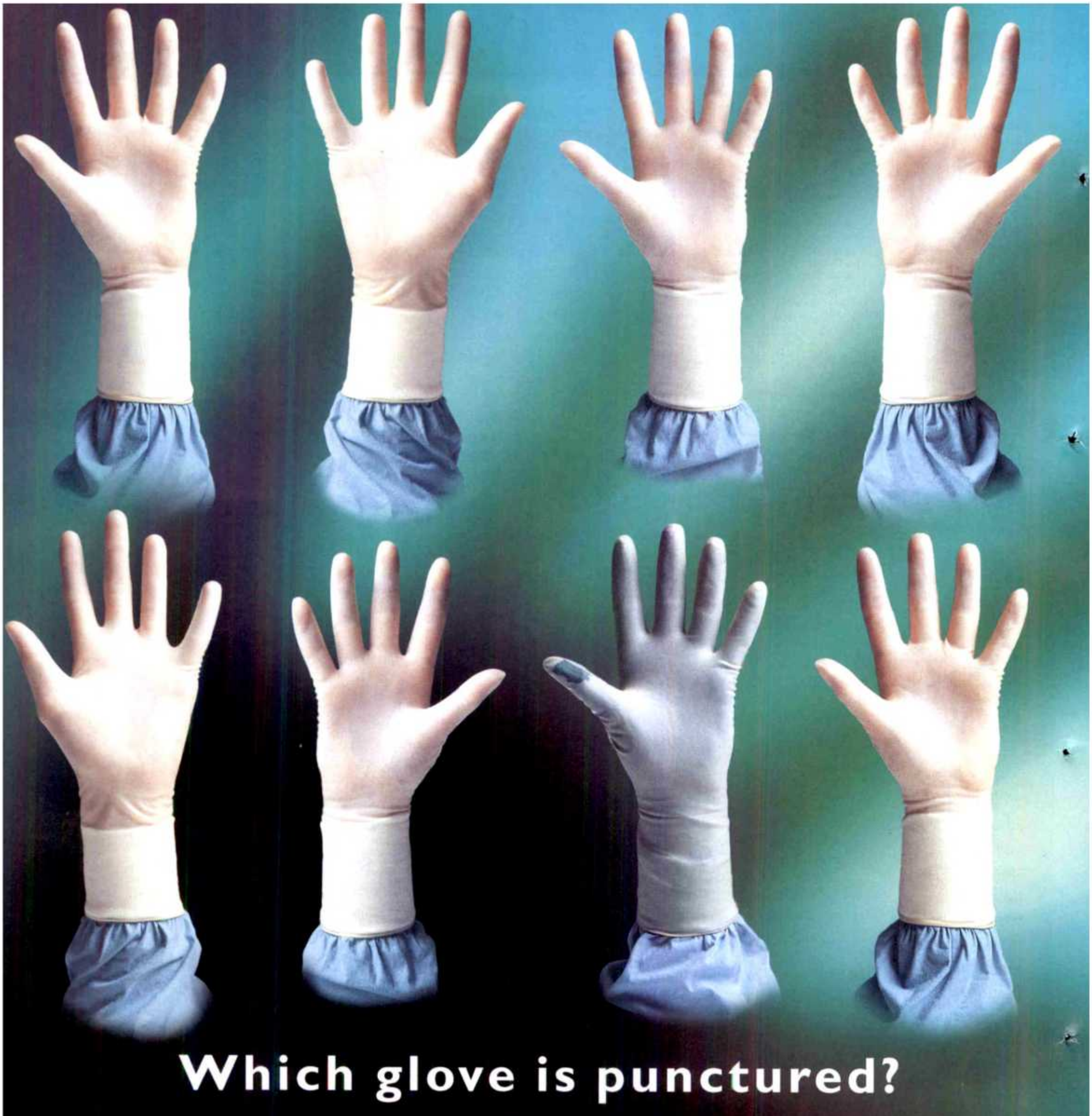

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Leading article

Perioperative nutrition of patients with gastrointestinal cancer

F. Bozzetti

Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy (e-mail: dottfb@tin.it)

The metabolic response to surgical trauma is mainly characterized by an increase in basal metabolic rate, a negative nitrogen balance, increased gluconeogenesis and increased synthesis of acute-phase proteins. These reactions are probably a result of evolution and are aimed at ensuring the availability of endogenous substrates for glucose-dependent tissues, such as bone marrow, brain and healing wounds; the synthesis of acute-phase proteins enhances the scavenging process and helps repair. However, if for any reason this process is excessive or continues for too long, it leads to a progressive depletion of body compartments and to a multiorgan functional impairment, with a consequent adverse clinical outcome. Obviously, the severity of such depletion is magnified if the patient is starving and the consumption of lean body mass is not compensated by an exogenous supply of nutrients, or if the patient is already malnourished when surgical trauma occurs.

While the above metabolic reaction represents the traditional rationale for the nutritional support of surgical patients, especially if they are malnourished or are expected to face long-term starvation, the issue has recently been put in a different perspective. Data have shown that some early negative effects of starvation are not simply due to starvation *per se*, but to the starving of the gut, and early postoperative enteral nutrition (EN) has proven successful (compared with intravenous nutrition) in blunting the metabolic response after injury and improving protein kinetics, net balance and amino acid flux across peripheral tissue[1]. Furthermore, some authors have pointed out that postoperative infectious complications may result from immune suppression, of whatever origin (the disease itself, poor nutrition, surgical trauma, general anaesthesia, blood transfusion, etc.), and that such a state might be reversed to some degree by modulation of the immune response through specialized nutritional support. This could be achieved, regardless of the patient's nutritional status, by using immunonutrients as drugs.

Are these working hypotheses supported by an evidence-based science that demonstrates the potential of nutritional support in the perioperative period? What follows is an attempt to show how the results of the available randomized clinical trials (RCTs) fit with the above hypotheses. For the sake of clarity, the analysis will be limited to RCTs including only patients with gastrointestinal cancer, and an attempt will be made to differentiate studies of malnourished from studies of non-malnourished patients. Patients with cancer are, in fact, a rather homogeneous group, accounting for the highest proportion of patients undergoing elective gastrointestinal surgery in western countries; nutritional status is the major discriminant among the working hypotheses so far considered. In accordance with substantial literature, the definition of outcome-relevant malnutrition will be accepted as a recent non-volitional loss of 10 per cent or more of the usual bodyweight.

Perioperative nutrition in malnourished patients

In most RCTs of perioperative nutritional support of patients with gastrointestinal cancer, the degree of malnutrition varies considerably, ranging from no weight loss to weight loss exceeding 10 per cent. If the analysis is limited to those few RCTs[2,3] that included malnourished patients, a clinical benefit is noted in those randomized to total parenteral nutrition (TPN) compared with controls receiving standard isotonic fluids. The decrease in complication rate was from a mean of 56 per cent in the control arms to 34 per cent in the TPN arms, with no deaths in the latter group. However, in these patients nutritional support was begun 8–10 days before operation and continued for more than a week after surgery. These results are in agreement with those reported by von Meyenfeldt and colleagues[4] in a post-hoc analysis of a subgroup of malnourished patients with cancer who were treated with perioperative TPN or EN.

Recently a RCT has compared the effects of liquid immune-enriched diet (IED), containing omega-3-fatty acids, arginine and nucleotides, with a standard EN formulation in a three-arm study[5]. Arm 1 (preoperative and postoperative IED) and arm 2 (preoperative IED and postoperative EN) had similar complication rates, but arm 1 had fewer complications (18 per cent) than arm 3 (postoperative EN) (42 per cent). Both arm 1 and arm 2 had a shorter postoperative hospital stay than arm 3. From all of the above studies, it appears that postoperative nutritional support that begins in the preoperative period is beneficial in malnourished patients.

Postoperative nutrition in malnourished patients

Does nutritional support work even if it begins in the postoperative period, and which is better, EN or TPN? Unfortunately, studies in a really malnourished cancer population do not exist, but two large RCTs from Italy have compared prospectively two isoenergetic and isoprotein regimens, one by vein and the other by the enteral route. One study[6] randomized 241 patients (more than 90 per cent with gastrointestinal cancer) with moderate malnutrition to a daily regimen of 25 kcal/kg through TPN or EN. Major complications occurred in 40 and 38 per cent respectively. The Italian Society for Parenteral and Enteral Nutrition published the second and larger study[7] on 317 patients with moderate to severe malnutrition who received, for 1 week after operation, a similar calorie load but a higher nitrogen supply (a mean of 1·4 g amino acid per kg per day), beginning on the first postoperative day. Both complications and postoperative hospital stay were reduced in those receiving EN: 34 *versus* 49 per cent ($P < 0 \cdot 02$) and 13·4 *versus* 15·0 days ($P < 0 \cdot 009$) respectively.

Nutritional support in non-malnourished patients

There are ten other RCTs[8] of non-malnourished patients, or marginally malnourished patients, who received preoperative TPN (one EN) and in whom nutritional support was continued for a while during the postoperative period. Only half noted a reduction in complications. In contrast, no benefit and possible adverse effects have been reported in patients receiving TPN (*versus* standard intravenous fluids) after pancreatic surgery.

A different result appears in RCTs on immune nutrition; of nine studies comparing a perioperative or postoperative IED with EN or intravenous nutrition, published in the past decade[8], seven reported a benefit in terms of a reduction in the rate of infection or complications, or in length of hospital stay. Experience with perioperative IED, as well as some phase II trials, has prompted investigators[9] to consider that immune nutrition starting before operation and continuing into the postoperative period represents the best way of supporting patients. As for any other substance with supposed pharmacological action, immunonutrients must reach adequate tissue and plasma levels to be active and this is easier if provision of IED is begun before surgery.

Conclusion

What should be done for malnourished patients with gastrointestinal cancer undergoing elective surgery? From RCTs there is evidence that:

1. Nutritional support (TPN, EN, IED) beginning 7–10 days before operation and continuing after surgery is able to decrease complication rates, compared with postoperative standard intravenous fluids or EN alone. Both TPN and IED have been shown to result in a decrease of 22–24 per cent in complication rate; TPN was delivered in hospital whereas IED was given to outpatients awaiting admission.
2. If patients are to be treated only in the postoperative period (to avoid a long preoperative hospital stay), EN appears to be a better choice than TPN provided that nitrogen intake is adequate.

In non-malnourished patients, the effect of perioperative TPN is neither constant nor predictable, and postoperative TPN alone may do more harm than good. Postoperative IED, however, seems to work well, in contrast to the recommendations of a recent American summit[10] that suggested IED solely for malnourished patients.

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Leading article

Wound healing

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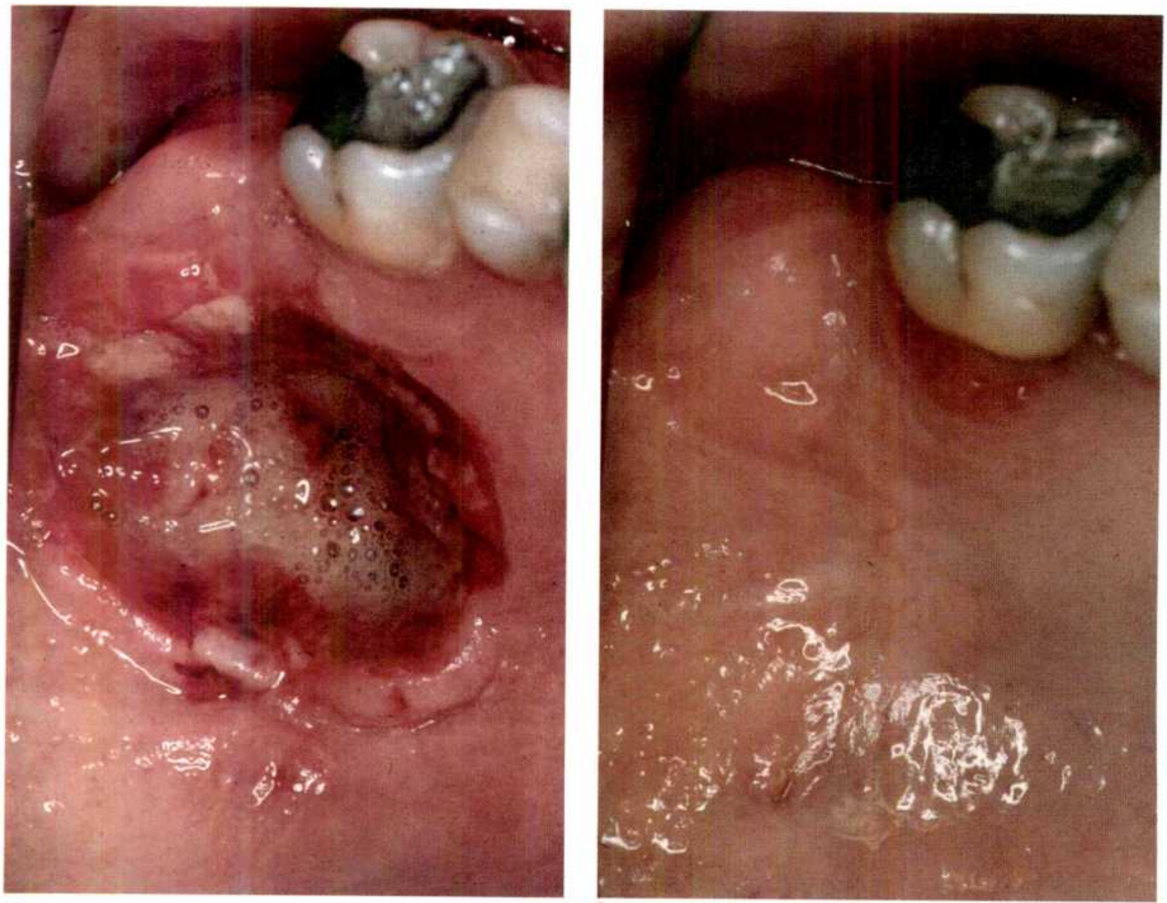
Surgeons produce wounds on a daily basis and the majority heal without complication. Still, clinical problems do arise and the biological basis of healing is not appreciated by all clinicians. In the UK, wounds cost the National Health Service £1 billion a year and, although a large proportion of this cost is due to inappropriate delivery of care, modification of systems of care will provide only part of the answer to this clinical challenge. The biological basis of repair following wounding involves a complex series of events including cell proliferation, migration, differentiation and remodelling. While tissue regeneration occurs in lower vertebrates, in higher vertebrates wound healing is essentially a fibroproliferative response that usually leads to scarring[1]. A clinical spectrum of wound healing exists in humans. At one end is 'excessive healing', with fibrosis and the deposition of excessive scar tissue, for example adhesions and keloid scars. At the other end of the spectrum are wounds that either completely fail to heal or exhibit delayed healing; such problems may occur in situations as diverse as fracture non-union, breakdown of anastomoses and chronic skin ulcers.

Recent advances in the management of both chronic and acute wounds have come from a greater understanding of the central mechanisms that control normal wound healing. Studies of fetal wounds, which heal without scarring, have demonstrated differences in growth factor profiles from those of adult wounds; transforming growth factor (TGF) β is of particular interest[2]. Subsequent research has established the pivotal role of TGF-β and, more recently, of connective tissue growth factor (CTGF), which is regulated downstream from TGF-β; these factors are involved in the deposition of excessive extracellular matrix after injury in situations as diverse as glaucoma surgery and gingival hyperplasia[3]. Available data suggest that the processes of tissue repair are determined by intrinsic (tissue specific) and extrinsic (extent of wounding, wound microflora) factors associated with the injury. While good surgical technique (debridement, careful closure, avoidance of excessive tension and ischaemia) will minimize inflammation at the wound site, other steps may now be considered. Agents have been identified that can be applied at the time of injury to inhibit cellular recruitment, inflammation and subsequent fibrosis. Much of this work has been pioneered in ophthalmic surgery, where scarring, should it occur, may have devastating consequences. Already, several compounds have been developed for clinical use. Initial work showed that single applications of 5-fluorouracil (an antimitotic agent) decrease initial fibroblast responses[4] and researchers are now investigating antibodies to CTGF in this situation as another means of decreasing fibrosis following surgery.

Reducing inflammation and growth factor activity may reduce scarring, but what about the reverse? Considerable research has gone into the application of exogenous growth factors in attempts to stimulate healing. So far, however, despite much investment, only one product using recombinant platelet-derived growth factor has been approved for clinical use (in uninfected neuropathic diabetic foot ulcers). Several clinical studies have found that the healing rate of such ulcers has improved from 30 to 50 per cent at 3 months. These results of exogenous growth factor application are less impressive than those in animal models of wounding; this has been attributed to the protease-rich nature of the fluid present with chronic ulcers, which is derived from resident cells and bacteria within the wound. The role of matrix metalloproteinases (MMPs), which regulate the turnover of collagen and extracellular matrix in health, has attracted particular attention. The balance between MMPs and their inhibitors appears crucial in achieving successful wound healing. Attempts have been made to inhibit the function of these proteases pharmacologically, with both specific and non-specific inhibitors, but this form of management is yet to have a proven value in clinical practice.

Site- and age-specific variations in wound healing are evident clinically. It is interesting that intraoral mucosal wounds, much like fetal wounds, exhibit privileged healing with rapid remodelling and minimal scar formation (*Fig. 1*). While this phenomenon is related, in part, to differing wound environments (moisture, temperature, tension) between tissue sites, phenotypic and genotypic differences between cell populations in wounds are also clearly important[5]. In aged skin, changes in structure within the extracellular matrix and biochemical cellular responses to injury contribute, paradoxically, to both delayed healing and improved scarring. The role of sex hormones in mediating these alterations is becoming increasingly apparent[6].



a Day 7 **b** Day 56

Fig. 1 Preferential healing of adult oral mucosa after operation. **a** Seven days after injury; **b** 56 days after injury

Fig. 2 Non-allergenic allograft material

In addition to modulating the wound environment, research in chronic and acute wound healing is now inextricably linked with developments in tissue engineering. Techniques to replace tissue lost through acute injury or burns have historically relied solely on grafting, but developments in keratinocyte culture and the use of substitute skin matrices now have the potential to provide alternative treatments[7]. These matrices (composed of a variety of synthetic resorbable polymers and/or normal extracellular matrix components of the dermis, such as collagen and hyaluronan) are available in several forms containing fibroblasts and keratinocytes. The concept of a non-allergenic allograft material provided commercially is now a reality (*Fig. 2*). Furthermore, an opportunity exists to engineer matrices containing pluripotent stem cells; future developments in this area may have a significant impact on clinical practice.

While scientific discoveries offer potential new therapies for chronic wounds, the basic principles of surgical technique remain pivotal in initiating healing. Both clinicians and patients should recognize the value of surgical and non-surgical interventions in non-healing wounds, and strenuous attempts should be made to provide a clinical service where patients can be assessed and treated appropriately. Examples already exist in dedicated leg ulcer and diabetic foot clinics; their value is undoubted in achieving healing of chronic wounds. Extension of such clinics to provide comprehensive care for a wide range of patients with healing difficulties has occurred in both the USA and Europe[8]. Such centres can not only provide a clinical service, but also undertake education and research; a professional approach to, and comprehensive understanding of, the problems of wound healing is achieved.

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CHANGE OF PUBLISHER

From volume 90, issue 1, January 2003, the *British Journal of Surgery* will be published by John Wiley & Sons Ltd.

Therefore from **Monday 9 September 2002** all papers and correspondence should be sent to:

The Editor, *BJS*, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester PO19 8SQ, UK. Telephone: +44 (0) 1243 779777. Facsimile: +44 (0) 1243 775878.

Complications of radiofrequency coagulation of liver tumours

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Background: Radiofrequency coagulation (RFC) is being promoted as a novel technique with a low morbidity rate in the treatment of liver tumours. The purpose of this study was to assess critically the complication rates of RFC in centres with both large and limited initial experience, and to establish causes and possible means of prevention and treatment.

Methods: This is an exhaustive review of the world literature (articles and abstracts) up to 31 December 2001; 82 independent reports of RFC of liver tumours were analysed.

Results: In total, 3670 patients were treated with percutaneous, laparoscopic or open RFC. The mortality rate was 0·5 per cent. Complications occurred in 8·9 per cent: abdominal bleeding in 1·6 per cent, abdominal infection in 1·1 per cent, biliary tract damage in 1·0 per cent, liver failure in 0·8 per cent, pulmonary complications in 0·8 per cent, dispersive pad skin burn in 0·6 per cent, hepatic vascular damage in 0·6 per cent, visceral damage in 0·5 per cent, cardiac complications in 0·4 per cent, myoglobinaemia or myoglobinuria in 0·2 per cent, renal failure in 0·1 per cent, tumour seeding in 0·2 per cent, coagulopathy in 0·2 per cent, and hormonal complications in 0·1 per cent. The complication rate was 7·2, 9·5, 9·9 and 31·8 per cent after a percutaneous, laparoscopic, simple open and combined open approach respectively. The mortality rate was 0·5, 0, 0 and 4·5 per cent respectively.

Conclusion: The morbidity and mortality of RFC, while low, is higher than previously assumed. With adequate knowledge, many complications are preventable.

Paper accepted 17 April 2002

British Journal of Surgery 2002, **89**, 1206–1222

Introduction

Radiofrequency coagulation (RFC) is one of several competing interstitial therapies that have recently been developed for the focal treatment of inoperable liver tumours. The purpose of this study was to assess the nature and the rate of complications, including mortality, of RFC of liver tumours from centres with both large and limited initial experience. It was also hoped to establish causation and to comment on prevention and treatment.

Patients and methods

An exhaustive *Current Contents* search was carried out for the period from 1 January 1990 to 31 December 2001 using the keywords '(radiofrequency, radio-frequency or radio frequency) and (liver or hepatic or hepatocellular)' without exclusion of any language. All abstract books from the same period published in *Radiology*, *American Journal of Radiology*, *Journal of Vascular and Interventional Radiology*, *European Radiology* and *Surgical Endoscopy* were searched manually. Furthermore, relevant papers were identified from the reference lists of papers previously obtained through the search. Abstracts from recent international meetings were also analysed. Short reports were not excluded. The authors of one recent large study were contacted for more details concerning their abstract[1].

In cases where the patient population of two or more reports overlapped, only the most detailed report was retained. Reports describing complications without specifying the size of the patient population were excluded from the calculation of global and specific complication rate, but were still included in the discussion of each type of

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

complication. Common side-effects of RFC, such as pain, fever and nausea (the post-RFC syndrome, present in 87 per cent of patients[2]), as well as an asymptomatic right pleural effusion[3], were not regarded as complications.

Results

Eighty-two reports[1,4–84] were included in the analysis. In total, 3670 patients were treated with percutaneous, laparoscopic or open RFC. The overall complication rate was 8·9 per cent (*Table 1*). The mortality rate was 0·5 per cent (*Table 2*). The complication rate was similar for the percutaneous (7·2 per cent), laparoscopic (9·5 per cent) and simple open (9·9 per cent) approaches (*Table 3*). However, patients treated by open RFC combined with cryotherapy, hepatic or extrahepatic resection had a much higher morbidity rate (31·8 per cent). The mortality rate was 0·5, 0·0 and 4·5 per cent respectively.

Bleeding

Clinically significant intraperitoneal bleeding after RFC occurred in 24 instances, one of which was fatal[1]. Bleeding was not limited to treatment of hepatocellular carcinoma (HCC)[19,53,55,62,85], but occurred also in liver metastases[18,73,74]. It originated from an incompletely coagulated subcapsular tumour, from a bleeding electrode track, from a tear in the liver parenchyma[53], from a hepatic rupture due to an intrahepatic haematoma[10] or from delayed rupture of a hepatic artery pseudoaneurysm[86]. Treatment was mainly conservative; one embolization[86] and four surgical interventions[10,18,53,62] were described. Bleeding did not occur in any of 278 patients after cauterization of the electrode track, but occurred in ten (0·9 per cent) of 1154 patients who had no cauterization. It occurred in one (0·3 per cent) of 332 patients after open and laparoscopic procedures, and in 22 (0·8 per cent) of 2898 after percutaneous procedures. No bleeding was noted in 26 patients in whom the track was filled with gelatin sponge[5,43].

Intrahepatic and subcapsular haematoma

A subcapsular haematoma (*Fig. 1*) was most often found after RFC of subcapsular tumours[41,55]. Intrahepatic (*Fig. 1*) and subcapsular haematoma occurred after treatment of both HCC[20,55] and liver metastases[30,41,47,74]. Treatment of this complication was mainly conservative, with therapeutic embolization described in three patients[20,25,41] and surgery in two[10,81].

Hepatic abscess

Thirty-four hepatic abscesses (*Fig. 2.*), two of which were fatal[1,81], have been reported after RFC[1,9,15,22,32,33,46,81,84]. One abscess developed only after 5 months[81,87]. Treatment consisted of percutaneous drainage and intravenous antibiotics[33,81,84,88]. At least eight patients who developed an abscess had an alteration of the biliary system: four had a biliary stent[9,22], three a bilioenteric anastomosis[22,33], and one a bile duct stricture[81].

Peritoneal infection

One fatal case of *Staphylococcus aureus* peritonitis[53] and one fatal case of infected ascites[80] were reported. The former complication was attributed to a disruption of sterile technique.

Biliary tract damage

A biliary stricture was reported in 18 patients[1,10,14,16,22,56,81,84], one of whom died[1]. Seven peripheral strictures[14,16,22] were clinically asymptomatic. Central biliary strictures complicating RFC of hilar tumour[16,56,81,84,89,90] cause cholestasis and require a stent[56,81,84,89]. Strictures may be complicated by an abscess[81], a biliovenous fistula[16], or lead to partial hepatic atrophy[16]. Strictures may become evident as late as 4 months after RFC[56]. There were seven biliomas[1,16,64,70] and six cases of bilioperitoneum[10,22,32]. Three of the bile leaks were attributed to a direct electrode injury of the main bile ducts[10]. Three reports of haemobilia were found[30,53,84], one starting during RFC[91] and another occurring 6 days after the procedure[30]. Other biliary tract damage included a biliocutaneous fistula[5] and a fatal bile leak into the chest[32]. The rate of biliary complications was similar in patients treated by RFC without a Pringle manoeuvre (25 (0·8 per cent) of 3227)[1,5,10,14,22,30,32,53,70,81] and with a Pringle manoeuvre (one (0·6 per cent) of 159)[26,34,37,46,56,59,92,93].

Liver failure

Seven instances of fatal liver failure were reported[1,10,15,22,64,81]. Four were due to central vascular thrombosis[1,22,64] and three to overestimation of liver reserve[1,10,81]. A transient mild deterioration of liver function was noted in 22 patients[10,12,20,27,47,58,59,64,66]. Child–Pugh grade increased by one to three points but returned to the preprocedural value within 2 weeks in most, but not all, patients.

Table 1 Complications of radiofrequency coagulation in 3670 patients

Complication	No. of patients	References
Abdominal bleeding	60 (1·6)	
Intraperitoneal bleeding	24 (0·7)	1, 9, 10, 18, 19, 22, 38, 53, 55, 62, 73, 74
Intrahepatic haematoma	6 (0·2)	10, 20, 25, 30, 39
Subcapsular haematoma	20 (0·5)	5, 9, 20, 22, 32, 41, 47, 55, 74, 81
Abdominal wall bleeding	1 (0·0)	20
Abdominal wall haematoma	6 (0·2)	20, 48, 58
Non-specified haematoma	3 (0·1)	15, 46
Abdominal infection	42 (1·1)	
Hepatic abscess	34 (0·9)	1, 9, 15, 22, 32, 33, 46, 81, 84
Wound infection	4 (0·1)	10, 56, 64
Peritoneal infection	2 (0·1)	53, 80
Unspecified sepsis	2 (0·1)	1
Biliary tract damage	38 (1·0)	
Biliary stricture	18 (0·5)	1, 10, 14, 16, 22, 56, 81, 84
Bilioma	7 (0·2)	1, 16, 64, 70
Bilioperitoneum	6 (0·2)	10, 22, 32
Haemobilia	3 (0·1)	30, 53, 84
Biliovenous fistula	2 (0·1)	16
Biliocutaneous fistula	1 (0·0)	5
Biliopleural fistula	1 (0·0)	32
Liver failure	29 (0·8)	
Fatal liver failure	7 (0·2)	1, 10, 15, 22, 64, 81
Mild liver failure	22 (0·6)	10, 12, 20, 27, 47, 58, 59, 64, 66
Pulmonary	29 (0·8)	
Pneumothorax	10 (0·3)	1, 20, 32, 47, 49, 61
Symptomatic pleural effusion	7 (0·2)	20, 22, 53, 74
Haemothorax	5 (0·1)	1, 9, 45, 53
Pneumonia	5 (0·1)	22, 46, 64
Pulmonary embolus	1 (0·0)	64
Adult respiratory distress syndrome	1 (0·0)	15
Dispersive pad skin burn	21 (0·6)	1, 5, 10, 15, 22, 32, 34, 78
Hepatic vascular damage	22 (0·6)	
Portal vein thrombosis	9 (0·2)	1, 14, 22, 30, 46, 55, 64
Hepatic vein thrombosis	2 (0·1)	16, 32
Hepatic artery damage	9 (0·2)	1, 16, 22, 46, 66
Hepatic infarction, unspecified	2 (0·1)	15, 71
Visceral damage	19 (0·5)	
Cholecystitis	5 (0·1)	27, 53, 57, 66
Diaphragmatic burn	5 (0·1)	1, 25, 32, 54, 81
Colonic burn	2 (0·1)	32, 74
Gastric burn	1 (0·0)	1
Jejunal burn	1 (0·0)	74
Renal burn	2 (0·1)	1, 54
Abdominal wall burn	2 (0·1)	10, 81
Non-specified damage	1 (0·0)	46
Cardiac	15 (0·4)	
Arrhythmia	10 (0·3)	1, 5, 10, 20, 24, 59, 72, 81
Myocardial infarction	2 (0·1)	5, 81
Heart failure	3 (0·1)	10, 56
Myoglobinaemia and myoglobinuria	8 (0·2)	
Myoglobinaemia	3 (0·1)	70
Myoglobinuria	5 (0·1)	10
Renal failure	4 (0·1)	39, 46, 48, 81
Seeding	7 (0·2)	24, 25, 55, 74
Coagulopathy	6 (0·2)	
Thrombocytopenia	5 (0·1)	10, 56
Hypoprothrombinaemia	1 (0·0)	20
Hormonal	4 (0·1)	
Carcinoid crisis	2 (0·1)	33, 81
Hyperglycaemia	1 (0·0)	33
Addisonian crisis	1 (0·0)	33

Table 1 Continued

Complication	No. of patients	References
Miscellaneous	9 (0·2)	
Central hyperthermia	2 (0·1)	20, 48
Brachial plexopathy	2 (0·1)	70
Oesophageal variceal bleeding	1 (0·0)	55
Gastrointestinal bleeding	1 (0·0)	72
Transient ischaemic attack	1 (0·0)	1
Difficult removal of electrode	1 (0·0)	69
Pseudoaneurysm of abdominal wall	1 (0·0)	1
Unspecified, minor	14 (0·4)	53, 74
Total	327 (8·9)	

Values in parentheses are percentages

Table 2 Mortality in 3670 patients undergoing radiofrequency coagulation

Cause of death	No. of patients	References
Sepsis	7 (0·2)	
Staphylococcus aureus peritonitis	1	53
Infected ascites	1	80
Biliopleural fistula	1	32
Hepatic abscess with diaphragmatic necrosis	1	81
Hepatic abscess	1	1
S. aureus chest infection	1	46
Unspecified sepsis	1	1
Liver failure	7 (0·2)	
Portal vein thrombosis	3	1, 22, 64
Hepatic infarction	1	15
Extensive resection	1	81
Extensive coagulation	1	10
Advanced liver cirrhosis	1	1
Cardiac complications	4 (0·1)	
Carcinoid crisis	2	33, 81
Cardiac arrest	1	59
Myocardial infarction	1	5
Peritoneal haemorrhage	1 (0·0)	1
Bile duct stricture	1 (0·0)	1
Total	20 (0·5)	

Values in parentheses are percentages

Pulmonary complications

Ten pneumothoraces were noted[1,20,32,47,49,61], mostly after an intercostal percutaneous approach. Seven symptomatic pleural effusions occurred[20,22,53,74]. Five haemothoraces were due to damage of an intercostal vessel by the electrode[1,9,45,53]. On ultrasonography, gas bubbles are frequently seen in the liver veins and in the right atrium, but pulmonary gas emboli have never been reported[68,91]. Five pneumonias[22,46,64] were reported, one of which was fatal[46]. Adult respiratory distress syndrome occurred only once[15].

Dispersive pad skin burns

Twenty-one instances of, mostly, first- and second-degree but also third-degree skin burns near or under the dispersive pad have been noted[1,5,10,15,22,32,34,78] (*Fig. 3*). They occurred using Radiotherapeutics®, (Sunnyvale, California, USA)[5], RITA® (RITA Medical Systems, Mountain View, California, USA)[10,78] and Radionics® (Burlington, Massachusetts, USA)[34,90,94,95] electrodes. In most reported burns, either high power (greater than 50 W) had been used[5,34,94,95], the procedure was long (more than 10 min)[34,94,95] or only one standard dispersive pad (100 cm^2)[34,90] had been placed. Several authors mentioned disappearance[34,94] or decrease[95] of the rate of skin burns after placing more or larger pads.

Portal vein thrombosis

Nine portal vein thromboses were reported[1,14,22,30,46,55,64], three of which proved fatal[1,22,64]. Segmental portal thrombosis may remain asymptomatic[86]. Factors predisposing to portal vein damage are central location of the tumour close to the portal vein[1,64,68], compression of the vein by the tumour[96] and accidental puncture by the electrode. A higher rate of portal vein thrombosis occurred after a Pringle manoeuvre than when no such manoeuvre had been carried out. Of 3227 patients treated with RFC with normal liver blood flow, seven cases of portal vein thrombosis[1,14,22,30,55] were described (0·2 per cent of cases). In 188 patients treated with RFC with a Pringle manoeuvre[26,34,37,46,56,59,64,68,92,93], four cases of portal vein thrombosis[46,64,68] were reported (2·1 per cent of cases). A short (2–3 min) Pringle manoeuvre in the middle of the RFC procedure caused no thrombosis in a series of 92 patients[92], in contrast to four cases (4·2 per cent) in 96 patients when the manoeuvre was sustained throughout the whole RFC procedure[26,34,37,46,56,59,64,68,93].

Table 3 Complication rate of radiofrequency coagulation according to approach

	Percutaneous (*n* = 2898)	Laparoscopic (*n* = 168)	Simple open (*n* = 142)	Combined open* (*n* = 22)
Intraperitoneal bleeding	22 (0·8)	1 (0·6)	0 (0)	0 (0)
Intrahepatic haematoma	4 (0·1)	0 (0)	0 (0)	0 (0)
Subcapsular haematoma	18 (0·6)	1 (0·6)	0 (0)	0 (0)
Abdominal wall bleeding or haematoma	2 (0·1)	5 (3·0)	1 (0·7)	0 (0)
Abdominal infection	31 (1·1)	0 (0)	0 (0)	1 (4·5)
Biliary tract damage	16 (0·6)	0 (0)	6 (4·2)	1 (4·5)
Liver failure	11 (0·4)	2 (1·2)	3 (2·1)	0 (0)
Pulmonary complications	17 (0·6)	2 (1·2)	0 (0)	1 (4·5)
Pad skin burn	18 (0·6)	0 (0)	0 (0)	0 (0)
Hepatic vascular damage	13 (0·4)	0 (0)	3 (2·1)	1 (4·5)
Visceral damage	14 (0·5)	0 (0)	0 (0)	0 (0)
Cardiac complications	8 (0·3)	1 (0·6)	0 (0)	1 (4·5)
Myoglobinaemia and myoglobinuria	3 (0·1)	1 (0·6)	0 (0)	0 (0)
Renal failure	0 (0)	1 (0·6)	0 (0)	1 (4·5)
Seeding	8 (0·3)	0 (0)	0 (0)	0 (0)
Coagulopathy	0 (0)	0 (0)	0 (0)	1 (4·5)
Hormonal complications	3 (0·1)	0 (0)	0 (0)	0 (0)
Miscellaneous	6 (0·2)	2 (1·2)	1 (0·7)	0 (0)
Unspecified, minor	14 (0·5)	0 (0)	0 (0)	0 (0)
Total	208 (7·2)	16 (9·5)	14 (9·9)	7 (31·8)
Death	14 (0·5)	0 (0)	0 (0)	1 (4·5)

Only series detailing the total number of patients, the approach used, and the number and nature of all complications were included. Patients may have had more than one complication. *Open radiofrequency coagulation combined with cryotherapy, hepatic or extrahepatic resection

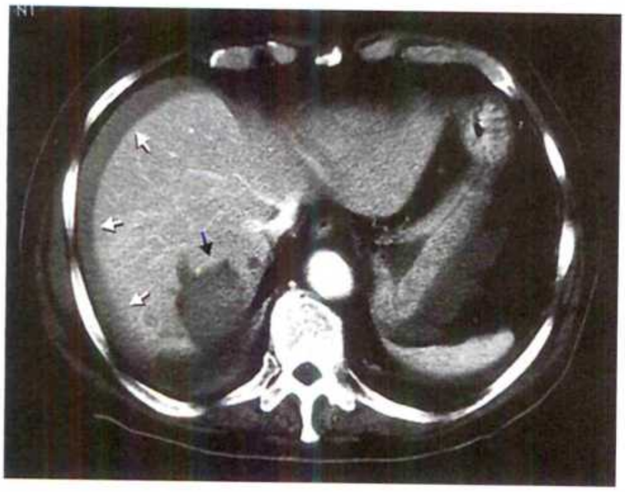

Fig. 1 Subcapsular haematoma (white arrows) and intrahepatic haematoma (black arrow) 24 h after percutaneous radiofrequency coagulation of a subcapsular colorectal metastasis in segment 7

Hepatic vein thrombosis

Only two instances of hepatic vein thrombosis causing peripheral infarction[32] or collateral vein development[16] have been observed.

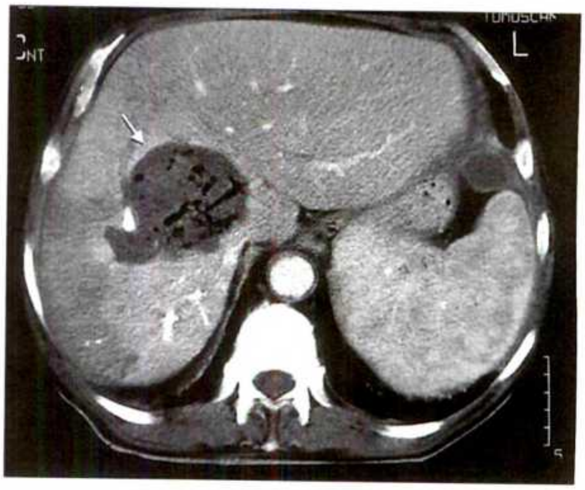

Fig. 2 Hepatic abscess (white arrow) 8 days after percutaneous radiofrequency coagulation of a hepatocellular carcinoma

Hepatic artery damage

Hepatic artery damage has been reported in nine patients[1,16,22,46,66]. One fatal and one non-fatal hepatic infarction[1] due to simultaneous hepatic artery and portal vein

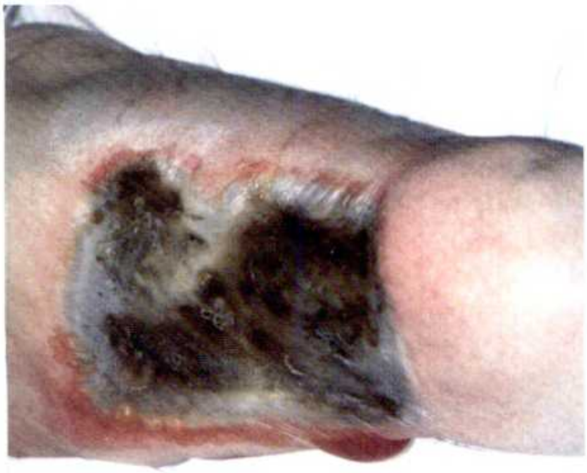

Fig. 3 Third-degree dispersive pad skin burn after a 2-h radiofrequency coagulation of a 10-cm melanoma metastasis using a 200-W generator with only one 100-cm^2 dispersive pad

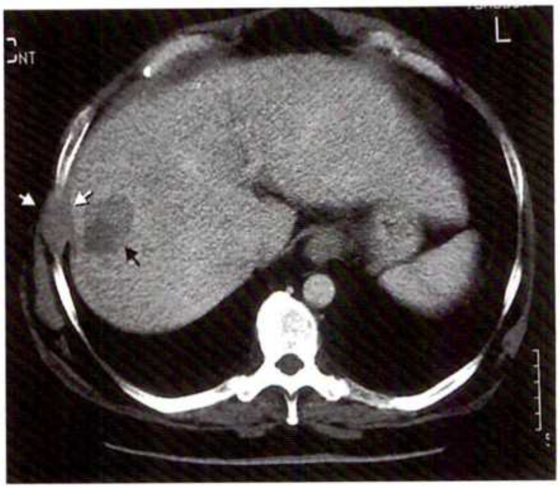

Fig. 4 Parietal wall seeding (white arrows) 1 year after direct percutaneous radiofrequency coagulation of a subcapsular hepatocellular carcinoma (black arrow). The electrode track had not been cauterized

thrombosis occurred after RFC of a central tumour. Three important arterioportal shunts[1,16] and two pseudoaneurysms[16,22] were noted. One intimal dissection of the hepatic artery without clinical sequelae was observed after balloon catheter occlusion[66].

Visceral damage

Visceral damage has occurred exclusively after percutaneous procedures. Five cases of post-RFC cholecystitis have been recognized[27,53,57,66] after coagulation near the gallbladder. All were treated conservatively. Diaphragmatic injury has been described in five of the series of 3670 patients[1,25,32,54,81], and in a further patient in another report[90] after RFC of a subdiaphragmatic tumour. Two burns were fatal as a result of bile leak into the chest[32] or an associated abscess[81]. Two other burns caused pain lasting for 10 days to 3 months[25,54]. Another patient sustained a diaphragmatic paresis[90]. Two colonic burns have been reported, one resulting in perforation[74] and one in fistula[32,95]. One jejunal perforation required operation[74], one gastric burn (*Fig. 4*) was due to RFC of a subcapsular tumour in the left lobe[1], and two renal burns were caused by RFC of a subcapsular tumour in segments 6 and 7[1,54]. Two abdominal wall burns have been reported, one during track coagulation[81] and one without coagulation[10].

Cardiac complications

Ten cases of rhythm disturbances were noted during or shortly after RFC: five vasovagal reactions or bradycardias[1,5,24] (one of which required cardiac massage[24] and another intravenous atropine[5]), one ventricular fibrillation treated by a single electrical discharge[20], two arrhythmias after RFC of carcinoid metastases[72,81], and one fatal cardiac arrest on day 20 after RFC[59]. Three patients with a pacemaker have undergone hepatic RFC[10,97]; malfunction was observed in one pacemaker[10]. Two instances of myocardial infarction were fatal; one was due to a carcinoid crisis[81] and the other was unrelated to the procedure[5].

Renal failure

Four instances of renal failure have been recorded[39,46,48,81]. One involved a *Staphylococcus aureus* chest infection[46], another a fatal carcinoid crisis[81], and a third was possibly caused by myoglobinuria[48].

Electrode track seeding

Seven cases of electrode track seeding (*Fig. 4*)[24,25,55,74,98] occurred in the series of 3670 patients, and a further three[99–101] were reported outside this series. Other unpublished cases have been referred to[102]. They occurred after RFC of HCC[24,55,98] and of colonic[74,99,100], pancreatic[25] and carcinoid[99,100] liver metastases. Seeding occurred after using monopolar[99,100,103,104], RITA[25,101] and Radionics[24, 55,74,98,102] electrodes. In one series of RFC of single HCCs[55], four instances of electrode track seeding after percutaneous RFC of a single HCCs in 32 patients were identified at 4, 6, 7 and 18 months after treatment. All four tumours were subcapsular and two were poorly differentiated. No cauterization of the electrode track had been used in these patients for fear of burning the abdominal wall.

Hormonal complications

Among the 3670 patients treated with RFC, 77 had endocrine liver metastases[7,9,10,18,26,27,32,33,38,39,41,48,50,68,72,79,81], 42 of which were carcinoid metastases[10,18,26,27,33,38,48,68,72,79,81]. In these 42 patients, two (4·8 per cent) fatal carcinoid crises occurred[33,81], both after debulking of extensive disease with RFC with or without cryotherapy. In one of them, the crisis started only after 40 h[33]. One patient with an insulinoma became temporarily hyperglycaemic and one patient with a cortisol-secreting tumour had a transient addisonian crisis[33].

Miscellaneous

Two cases of hyperthermia have been reported after a lengthy (175–420 min) RFC procedure; the core temperature rose to 38·8–40·2°C[20,48]. Difficulty in removing a RITA radiofrequency electrode, because coagulated tissue had become caught between the hooks and the shaft, has been reported twice (Reference 69; F. Meloni, personal communication, 1998).

Approach

The complication rate was similar for the percutaneous (7·2 per cent), laparoscopic (9·5 per cent) and simple open (9·9 per cent) approaches (*Table 3*). Patients treated by open RFC combined with cryotherapy, hepatic or extrahepatic resection had a morbidity rate of 31·8 per cent. The mortality rate was 0·5, 0, 0 and 4·5 per cent respectively. Of two patients treated by a thoracoscopic transdiaphragmatic approach[28,45], one developed pleural bleeding[45].

Discussion

The worldwide reported complication and mortality rates (7·2 and 0·5 per cent respectively) for percutaneous RFC in this cumulative series is higher than the 1·5 and 0·1 per cent rates reported previously in an Italian study[90], indicating that the complication risk of this rapidly spreading technique should not be underestimated. The true complication rate may be even higher than the rate calculated here, as some authors may have ignored minor complications. Furthermore, some late complications, such as bile duct strictures and electrode track seeding, may have been missed because of the short follow-up in many studies. Review of the available data has enabled the formulation of some recommendations on the prevention of complications and identification of risk factors.

Prevention of complications

Intraperitoneal bleeding

Cauterization of the electrode track[17,18,24,44,56,64,81,96,105–109] can be strongly recommended for all patients, to prevent both oozing and significant bleeding. Cauterization is achieved by continuing power during slow withdrawal of the electrode after stopping the cooling for cooled electrodes[64,109] and after retraction of the prongs for expandable electrodes[68]. Oozing from the hepatic electrode track is noted in 30–34 per cent of patients[58,92]. Although oozing is most often limited to less than 7 ml blood[92,109], it has been incriminated as promoting seeding of viable tumour cells[55]. It can be prevented completely by cauterization[109]. Cauterization also effectively prevents post-RFC bleeding: no bleeding occurred in 214 patients having cauterization, compared with ten (1·0 per cent) of 1036 with no cauterization. While some apply cauterization only in cirrhotic liver[7,109], the present authors advise it in all patients as both oozing[109] and bleeding[73,74] have been noted in non-cirrhotic liver.

The recommendation of track cauterization for all patients has two important implications. The first is that general anaesthesia is recommended for all procedures, as coagulation of the most superficial part of the track within 2–3 cm from the hepatic capsule is often painful for patients who are under conscious sedation[55,110]. The second is that a perpendicular percutaneous approach is not advised for RFC of subcapsular tumours, as correct track cauterization using this route will lead to burns of the abdominal wall and skin[55,81].

In the authors' view, cauterization cannot be replaced by visual laparoscopic[58,111] or open[92] control of haemostasis. Coagulation of the point of entry of the electrode alone does not entirely prevent intraperitoneal bleeding, which occurred in one (0·3 per cent) of 332 patients after open and laparoscopic RFC, compared with 22 (0·8 per cent) of 2898 after percutaneous procedures. Furthermore, oozing is stopped rather than prevented, which is less ideal in the prevention of seeding. Experience with filling the electrode track with gelatin sponge[5,43] is too limited to draw meaningful conclusions.

Because of the risk of bleeding, the authors agree with most other workers in the field who recommend a postprocedural monitoring of haemodynamic variables for at least 4-6 h[8,20,50,59,65,78,85,91,105,112–116], only two authors settling for less[73,117].

Intrahepatic haematoma
An intrahepatic haematoma may be caused by accidental transgression of a large blood vessel[109]. Prevention lies in carefully avoiding hepatic vessels on the way to the tumour. Inadvertent injury to blood vessels may be more likely with triple-cooled and expandable electrodes, as it is impossible to visualize all prongs at the same time[118]. Straight electrodes may be advisable for tumours in the vicinity of several blood vessels[118].

Hepatic abscess
Bilioenteric anastomoses are known to increase the risk of septic complications after local treatment of liver tumours[119] as a result of retrograde enteric bacterial contamination of the biliary tract in up to 90 per cent of patients[120]. Germs found in abscesses after RFC, chemoembolization or percutaneous ethanol injection (PEI) in patients with bilioenteric anastomoses included *Escherichia coli*, *Clostridium perfringens*, streptococcus D and enterococcus[88,119]. Since the first description of abscesses after RFC, several groups[88,121,122] have started to give prophylactic antibiotics, although scientific proof of their value is unavailable at this time. A logical choice of antibiotics is amoxycillin plus clavulanic acid, which is active against all these organisms. In high-risk patients (previous biliary tract manipulation), a duration of 48 h has been suggested; otherwise one preprocedural intravenous dose is given[88].

Abscess after RFC is most likely when fever, leucocytosis and abundant intralesional gas are present[116,123]. Although the diagnosis is often obvious, several patients with an indolent course resulting in late diagnosis have been reported (malaise and a subfebrile state as the only symptoms)[124]. Intralesional gas is not synonymous with an abscess; gas bubbles in the coagulated area are seen in 63 per cent of computed tomography scans performed immediately after RFC[116]. At 1-month follow-up, however, gas should no longer be visible[116]. One abscess developed only after 5 months[81,87], suggesting that the devitalized tumour served as a nidus for delayed infection.

Peritoneal infection
It is clear that RFC should be performed with a strictly aseptic technique in a custom-designed environment.

Biliary tract damage
Experimental data suggest that the large bile ducts are protected from thermal damage by the cooling effect of the portal vein and the hepatic artery that run along them[124–126]. With intact blood flow, only small bile ducts associated with thrombosed blood vessels with a diameter of less than 3 mm are destroyed[125,126]. Damage to the larger bile ducts (adjacent to blood vessels greater than 3 mm in diameter) has never been observed[124,126]. Main bile duct stenosis has been noted only after RFC during a Pringle manoeuvre[124].

In clinical practice, however, intact blood flow does not decrease the risk of biliary complications. The fact that the number of reported biliary complications is limited is probably related to the warnings of this complication from the early days of RFC[52,111]. Most workers consider tumours closer than 1 cm to the main biliary ducts a contraindication to RFC[3,4,12,20,29,93,107,110]. However, two methods have recently been described to prevent biliary damage while treating central tumours[26,81]. One involved the prophylactic placement of a biliary stent in four patients having RFC of tumours near the major bile ducts; there were no complications[81]. The other involved the (successful) treatment of three central tumours while cooling the biliary ducts with chilled saline[26]. While these methods may decrease biliary damage, they may increase the risk of hepatic abscess formation. Prospective evaluation is needed.

Dispersive pad skin burns
As for electrocautery, the general recommendations for the placement of grounding pads[127–130] must be observed. Specific extra precautions need to be taken for RFC. Using electrocautery, one standard pad is sufficient as the current is limited (700 mA or less) and intermittent. Using RFC, the risk of burns with one pad is much higher, as current can be as high as 2000 mA and is applied continuously for one or more session of 10–20 min[131].

An excellent experimental study[131], using a 200-W generator for 10 min, studied the variables that influenced heating under the pad. On the basis of this study, the use of four (rather than one) 100-cm^2 pads is recommended to increase the dispersive surface. The pads should be placed horizontally to allow a longer leading edge. They should be equidistant from the electrode to prevent excessive heating of the nearest pad. A distance to the electrode of at least 50 cm should be observed as pad temperature rises with shorter distances. In practice, for 200-W generators the pads should be placed horizontally at the anterior and posterior aspect of the mid-thigh, 50 cm from the electrode[131]. This contrasts with earlier recommendations for low-power (50 W) generators[66,107] that advocated pads to be placed on the back. The above study, although extremely useful, does not allow any conclusion on the safety of procedures exceeding 10 min, or of serial procedures with short intervals. It is strongly recommended that manufacturers quickly develop a system of pad temperature monitoring with an automatic audible alarm and current shutdown. Meanwhile, temperature monitoring using thermistors sandwiched between the dispersive plate and the skin is advised[7].

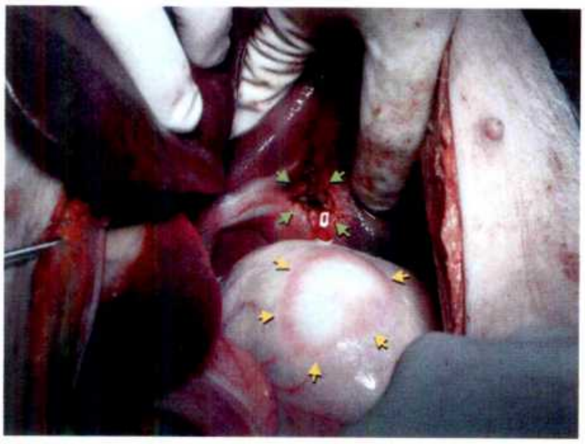

Fig. 5 Full-thickness stomach wall burn (yellow arrows) after a 12-min subcapsular radiofrequency coagulation (green arrows) at the undersurface of the left lobe of a pig liver without retracting the stomach

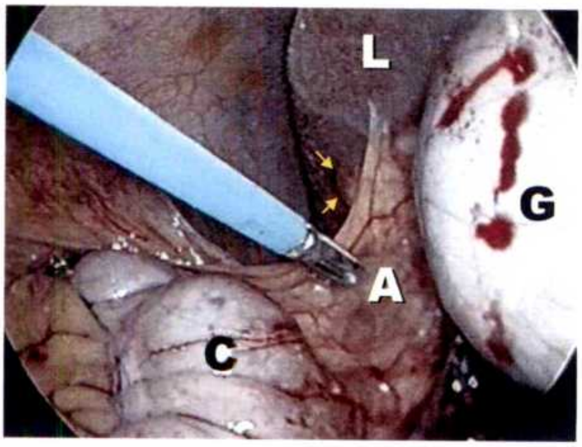

Fig. 6 The laparoscopic approach allows division of an adhesion between the transverse colon and a subcapsular segment 6 colorectal metastasis (yellow arrows) in order to avoid a colonic burn. A, adhesion; C, colon; G, gallbladder; L, liver

Portal vein thrombosis

In experimental studies, a Pringle manoeuvre enhances the risk of hepatic vessel thrombosis. After RFC with normal hepatic flow, vessels up to 3 mm show thrombosis[125,132]; 89 per cent of vessels with a diameter of 3–4 mm and 100 per cent of those with a diameter greater than 4 mm remain patent[125,133–135]. However, in experimental lesions produced with a Pringle manoeuvre, occlusive thrombosis has been observed even in large vessels (greater than 6 mm)[125,126]. The absence of protection of the endothelium by the cooling blood flow during the manoeuvre translates clinically into a higher rate of thrombosis of nearby portal vein branches. The authors refrain from any Pringle manoeuvre in circumstances of portal vein compression by the tumour. The available data also discourage a full manoeuvre for tumours within 1 cm of the main portal vein branches[64,68]. For such tumours a short (2–3 min) manoeuvre is an alternative that has until now never produced portal vein thrombosis[92]. A full Pringle manoeuvre for RFC of tumours at a distance from the main portal branches has, so far, never produced portal vein thrombosis.

Hepatic vein thrombosis, Budd–Chiari syndrome and inferior vena cava thrombosis

Hepatic vein thrombosis has been reported only twice[16,32]. Until now, no Budd–Chiari syndrome or inferior vena cava thrombosis has occurred after RFC, although both have been described after interstitial laser coagulation[14,136]. RFC of tumours in the fork between the inferior vena cava and one or more hepatic veins is probably safe, unless the veins are compressed by the tumour.

Hepatic artery damage

A small arterioportal shunt[14,116,137] is found in 25 per cent of patients when carefully looked for at computed tomography immediately after RFC[116]. It is seen as a wedge-like high-attenuation lesion during the hepatic arterial phase. Eighty per cent of arterioportal shunts have disappeared at the 1-month follow-up; the remaining 20 per cent are no longer visible at 4-month follow-up[116]. The majority of arterioportal shunts heal spontaneously and need only simple follow-up. Only one massive shunt[116] and one shunt associated with a growing pseudoaneurysm[16] have been reported so far; such shunts should be embolized. Embolization of all pseudoaneurysms[138] seems advisable, as they may experience delayed rupture with haemoperitoneum[86].

Visceral damage

A tumour closer than 1 cm to the gallbladder is a contraindication for a percutaneous procedure[12,29,110,139]. For tumours near the gallbladder, a laparoscopic or open approach allows cholecystectomy to avoid thermal cholecystitis or gallbladder perforation[96,107]. In contrast to other workers who remove the gallbladder before RFC[107], the authors prefer to remove it after RFC to prevent spillage of tumour cells that are still viable[96].

Burns of adjacent viscera have been predicted by a pig liver model, in which full-thickness burns of the stomach, small bowel and colon have been observed when the edge of the thermal lesion was less than 1 cm from the surface of the liver[125,134,140] (*Fig. 5*). In the light of this an open or laparoscopic approach has been advocated for subcapsular tumours within 2 cm of adjacent viscera[20,58,107,125,141]. This way, these organs can be protected by separating them from the liver surface (*Fig. 6*). In the absence of adhesions between the viscus and the liver, peritoneal saline instillation creating artificial ascites is being studied as an alternative[142].

Cardiac complications

The reports of rhythm disturbances stress the importance of continuous monitoring of vital signs and the presence of an anaesthetist during and for 1 h after the procedure, even if performed percutaneously[3,20,34,143,144]. Significant problems have been reported in patients undergoing RFC in a radiology suite without adequate anaesthesia[20]. Defibrillation devices should always be immediately available.

Hypotension

In experimental conditions, the combination of a pneumoperitoneum and clamping of the liver hilum may cause hypotension due to decreased venous return[145]. So far, this has not been reported in the clinical situation, but published experience with a Pringle manoeuvre during laparoscopic RFC is limited to four cases[21,37].

Acute renal failure

Only one case of acute renal failure, which may have been caused by myoglobinaemia, has been reported after RFC that lasted for 7 h[48]. However, the frequency of myoglobinaemia or myoglobinuria after RFC is probably underestimated. When looked for routinely, myoglobinaemia was found in three of ten patients being treated for large or multiple tumours[70]. Similarly, myoglobinuria has been reported in none of 25[146], and in five (6·6 per cent) of 76 patients[10], and was associated with RFC of very large (up to 15 cm) tumours[10]. In the near future, renal failure after RFC may become more frequent due to increasing coagulation diameter. More data are needed about the real prevalence and risk of myoglobinaemia. Until then, it is recommended that myoglobinaemia and myoglobinuria are measured routinely in situations of extensive coagulation to allow prompt recognition and preventive therapy (mannitol diuresis and alkalinization of the urine)[48]. Furthermore, a staged procedure should be considered for extensive disease[48].

Electrode track seeding

The risk of electrode track seeding has been the subject of recent debate[24,55,98,102,147–150] since one group noted this complication in 12·5 per cent of patients[55]. Most other workers report lower rates of seeding, from 0·2 per cent[90], 0·6 per cent[149], to 2·8 per cent[24]. The reasons for these differences are not clear. It may be that the real incidence of seeding is underestimated in many series with a short follow-up, as it may be recognized as late as 18 months after the procedure[55].

Several mechanisms may contribute to seeding. Viable tumour cells may adhere to a biopsy needle or to the electrode during its retraction. Tumour cells may also be carried into the track with a little bleeding. Furthermore, cells may be forced into the track by sudden intratumoral hyperpressure that is frequently encountered during RFC, audible as a popping sound. Finally, cells may be driven in when saline is injected into the tumour during or before RFC[151]. Incriminated risk factors for seeding are preprocedural biopsies[152,153], poor differentiation of the tumour[55], no cauterization of the electrode track[55], and a perpendicular approach to subcapsular tumours[55]. Some authors perform a preprocedural percutaneous[20,37,65,66,85,113,143,146], laparoscopic[7,111,121,154], or open[56] fine-needle or core biopsy of the liver tumour. However, a 5 and 25 per cent risk of tumour seeding have been reported for HCC and colorectal liver metastases respectively[152,153]. It therefore appears that biopsy proof of the nature of the tumour before RFC should be avoided when the clinical picture (history, imaging and tumour markers) is sufficiently diagnostic[3,85]. Poor differentiation of the tumour is a known risk factor for seeding after fine-needle aspiration biopsy and PEI[155], and is also associated with a higher risk of seeding after RFC[55].

Oozing after retraction of the electrode, which occurs in 30 per cent of cases[92], may promote seeding of viable tumour cells[55] and can be prevented completely by cauterization[109]. One group[55] systematically cauterized the electrode track, except for subcapsular tumours for fear of abdominal wall burns; all four cases of seeding occurred in patients with subcapsular tumours. Although unproven, the authors feel strongly that cauterization should be performed not only at the end of each RFC procedure, but also before every repositioning of the electrode. The seeding risk seems to be greater for subcapsular tumours, especially when a direct, perpendicular approach is used[148]. Once Glisson's capsule is breached, the tumour can bleed and cells can leak out immediately[102,156]. Furthermore, correct cauterization in this approach would lead to burns of the abdominal wall and skin[55,81]. An indirect oblique approach, through a sufficient layer of non-tumoral tissue, first aiming at the hilar pole of the tumour, is advised[148]. In this way the tumour is devascularized before it is coagulated, Glisson's capsule is coagulated only at the end, and cauterization of the intrahepatic track can be performed safely[24]. No seeding occurred in a series of 63 patients in which direct puncture of subcapsular tumours was avoided[148]. While some groups at this time consider a subcapsular location to be a contraindication to RFC, especially for patients awaiting transplantation[55,102,147], the present authors feel rather that a direct approach to these tumours is contraindicated. For subcapsular tumours, laparoscopy and laparotomy may often be the approach of choice, as they offer a greater degree of freedom for the indirect introduction of the electrode.

Haematogenous seeding

There is concern that RFC may increase the release of neoplastic cells into the circulation during the treatment, as has been observed after transarterial embolization[157]. In a recent study of 32 patients, tumour cells in peripheral blood were present in 34 per cent of patients just before RFC and in 44 per cent of patients 1 h after RFC[55]. No definite conclusion can be drawn because of small numbers. Furthermore, increased release of tumour cells in the bloodstream does not necessarily translate into increased haematogenous metastases.

Coagulopathy

A slight decrease in platelet count on the first day after RFC is common[3,154]. However, significant thrombopenia is rare after RFC, probably because there is no reperfusion, as in cryotherapy[146]. Platelet count less than 60 000 µl has been reported once after extensive RFC during 248 min[56]. The international normalized ratio usually shows little fluctuation in the postoperative period[154].

Hormonal complications

A carcinoid crisis is an extremely dangerous complication after RFC of a carcinoid tumour due to haemodynamic instability and cardiac rhythm disturbances. Patients should be monitored in the intensive care unit for at least 48 h after such a procedure and receive a prophylactic octreotide infusion[48,158]. Both recorded fatalities occurred after extensive procedures[33,81]; whether a staged approach for extensive disease is safer is not presently known.

Risk factors for complications

Complications after RFC for HCC are more common in Child–Pugh class C (27·6 per cent) than in class A (8·0 per cent) or class B (6·5 per cent)[20]. RFC of subcapsular tumours carries a higher risk of intraperitoneal bleeding, subcapsular haematoma, seeding and visceral damage; RFC of central tumours predisposes to biliary tract and central vessel damage. Thermal damage to neighbouring organs is found exclusively in the percutaneous approach. The same is true for seeding, probably because of the impossibility of coagulating the electrode track for superficial tumours using the percutaneous approach[55]. The laparoscopic approach has a complication pattern similar to that of the percutaneous approach, while avoiding seeding and visceral damage. Complication and mortality rates of open RFC combined with resection were not significantly different from those of hepatic resection alone for colorectal metastases (19 and 2 per cent respectively)[159]. Extensive procedures for large or multiple tumours carry a higher risk of liver failure, dispersive pad skin burn, myoglobinaemia or myoglobinuria, thrombocytopenia and central hyperthermia. Staged treatment should be considered for these patients.

Comparison with other interstitial techniques

Percutaneous ethanol injection

Several trials have compared PEI and RFC in the treatment of small (3 cm or less) hepatocellular cancers. In a prospective non-randomized trial, no complications occurred after PEI in 44 patients, whereas five complications occurred after RFC in 42 patients[91]. In a prospective randomized trial, no complications were observed after PEI in 50 patients or after RFC in 52[51]. In a comparative study that assessed seeding alone, seeding was observed after PEI in none of 100 patients, and in three of 28 patients after RFC[98]. This difference was attributed to the larger diameter (15–18 G) of radiofrequency electrodes compared with PEI needles, which increases bleeding during the procedure and so, in turn, seeding[55].

Cryotherapy

In a retrospective study comparing cryotherapy ($n = 130$) and RFC ($n = 14$), the complication rates were 17 and 0 per cent, thrombocytopenia rates 90 *versus* 0 per cent, and mean blood loss was 800 *versus* 40 ml respectively[106]. In a prospective non-randomized trial comparing intraoperative cryotherapy ($n = 54$) and RFC ($n = 92$), the complication rates were 41 and 3 per cent, and the mortality rates 2 and 0 per cent[146]. Brisk intraoperative haemorrhage from the cryoprobe track that required packing was encountered in almost 80 per cent of those undergoing cryotherapy; there was no instance of such haemorrhage after RFC. Intrahepatic abscess developed in 19 per cent after cryotherapy; no abscess developed after RFC. Renal failure occurred in 4 per cent after cryotherapy and in 0 per cent after RFC[146].

In contrast to cryotherapy, there is no reperfusion through injured blood vessels after RFC because vessels of up to 3 mm in diameter are coagulated along with the tumour[125,132]. There is therefore neither consumption of platelets nor activation of coagulation to cause a coagulopathy[146,160]. RFC probes are smaller than cryoprobes and their tracks can be coagulated during electrode withdrawal such that track bleeding is much less frequent[146]. Cracking of the parenchyma during thawing of the iceball, resulting in severe haemorrhage[160], is not relevant to RFC. Furthermore, the instantaneous coagulation of proteins and the absence of reperfusion in RFC result in a diminished release of toxic factors[161]. This explains why renal failure due to myoglobinuria occurred in only one (0·03 per cent) of 3670 patients after RFC, compared with 1·4 per cent after cryotherapy[162].

Laser

Complications after percutaneous interstitial laser therapy are similar to those after percutaneous RFC. In 676 patients, pleural effusion requiring drainage occurred in 2·2 per cent, subcapsular haematoma in 7·7 per cent, hepatic abscess in 0·9 per cent, peritoneal bleeding in 0·4 per cent, wound infection in 0·6 per cent, and bile duct injury in 0·3 per cent[163]. The mortality rate was 0·4 per cent. In a retrospective study comparing laser therapy ($n = 36$) and RFC ($n = 38$) for the percutaneous treatment of HCCs of up to 6 cm in diameter, no major complications were observed in either group[164].

Microwave

In a prospective randomized study comparing microwave ($n = 36$) and RFC ($n = 36$), the respective complication rates were 11 and 3 per cent[71].

Conclusion

The morbidity and mortality rates associated with RFC, while low, are higher than previously assumed. With adequate knowledge, many complications are preventable. It is conceivable that the complication rate may rise in the future when larger tumour volumes are coagulated by more powerful electrodes.

Acknowledgements

The authors thank Professor H. K. Lim for providing information additional to that in his abstract on complications of RFC in Korea[1].

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Tumour thickness as a predictor of occult lymph node metastases in patients with stage I and II melanoma undergoing sentinel lymph node biopsy

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Background: Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure used accurately to stage nodal basins at risk of occult metastases. There are no data as yet to show a survival benefit from SLNB and its use remains controversial. If Breslow thickness of the tumour correlates well with positive SLNB, it could be used to select patients for SLNB.

Methods: A quantitative systematic review of published studies on SLNB in patients with melanoma available by September 2001 was performed.

Results: Twelve studies containing 4218 patients with stage I and II melanoma were identified; 17·8 (95 per cent confidence interval 16·7 to 19·0) per cent of patients had nodal micrometastases detected by SLNB. The incidence of micrometastasis in sentinel nodes correlated directly with Breslow tumour thickness; it was 1·0 per cent for lesions of less than or equal to 0·75 mm, 8·3 per cent for 0·76–1·50 mm, 22·7 per cent for 1·51–4·0 mm and 35·5 per cent for more than 4·0 mm.

Conclusion: The Breslow thickness of primary melanoma predicts the presence of a sentinel node metastasis. The published data are not sufficient to demonstrate a correlation between other known prognostic indicators and a positive SLNB.

Paper accepted 28 June 2002

British Journal of Surgery 2002, **89**, 1223–1227

Introduction

The incidence of malignant melanoma is increasing worldwide[1]. The known prognostic variables for primary melanoma relate to histological characteristics (tumour thickness, ulceration, level of invasion), with a weaker effect of gender, age and site[2]. In the final version of the American Joint Committee on Cancer Staging System, Breslow thickness, the presence of ulceration, and the Clark's level for tumours less than 1 mm thick, are the only histological characteristics of the primary that are used to stage the tumour[3]. Multiple studies have confirmed that Breslow thickness has better predictive value than Clark's level[4–6] for all but thin tumours, for which Clark's level is an independent risk factor for relapse[7–9].

The commonest site of first recurrence of melanoma is in regional lymph nodes and so the status of the regional lymphatic basin is a powerful prognostic factor. Sampling lymph node basins by complete lymphadenectomy is an invasive surgical procedure with significant morbidity. Furthermore, elective lymph node dissection is not routinely practised as it has not been shown to have any beneficial effect on survival in primary melanoma[10]. Morton and his collaborators therefore introduced the technique of lymphatic mapping and sentinel lymph node biopsy (SLNB) as a minimally invasive procedure to permit accurate staging of nodal basins at risk of occult metastases[11]. The technique, when SLNB is negative, is associated with less morbidity than complete lymphadenectomy, but it remains an expensive procedure with some morbidity. As there are no data so far to show a survival benefit from SLNB, its use remains controversial[12] and there is a perceived need to determine optimal patient selection.

Some authors have suggested that Breslow thickness predicts the presence of micrometastases in sentinel nodes[13]. If Breslow thickness of the tumour correlates well with node positivity, it could be used to select patients for SLNB. The objective of the present study was to determine the degree to which Breslow thickness predicts the presence of sentinel node micrometastases in patients with primary melanoma, potentially allowing selection of patients for lymphatic mapping and SLNB.

Methods

The aim was to identify all relevant papers on SLNB in primary melanoma available by September 2001.

Inclusion criteria

All studies that met the following criteria were included: studies of SLNB in patients with primary melanoma stage I and II; patients categorized according to the Breslow thickness categories used in the previous version (1997) of the American Joint Committee on Cancer Melanoma Staging System (less than or equal to 0·75, 0·76–1·50, 1·51–4·0 and more than 4·0 mm); the rate of positive sentinel lymph nodes reported; the study included 100 or more patients.

Search strategy

A computerized search was performed to identify all registered articles on the subject published by September 2001. Studies were identified through sensitive electronic searches of Medline (from 1966 to September 2001) and Embase (1974 to September 2001) using the recommended Cochrane Collaboration search strategy with MeSH headings 'melanoma' and 'sentinel lymph node' including all subheadings. The reference lists of all relevant retrieved papers and review articles were scanned to identify other eligible studies not found by computerized database searching. Authors were contacted to verify the data and obtain additional information. If there was more than one study report, authors were asked whether the patient groups overlapped. Ongoing and unpublished studies were identified, but their results are not included. The search was restricted to articles published in the English language.

Data extraction

The following data were extracted independently from each included study: total number of patients; number of patients according to the thickness group; number of SLNB-positive patients and number of SLNB-negative patients for each thickness group.

Statistical analysis

The proportions for each thickness group were calculated with standard errors using Confidence Interval Analysis software (BMJ Bookshop, London, UK). χ^2 test for trend was calculated using EpiInfo 2000 software (Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Results

Some 417 articles were retrieved that reported SLNB in patients with melanoma and 22 articles met the inclusion criteria. Ten of these 22 were excluded as they reported results on the same patient populations as the 12 included patients, but at different time intervals. The more recent of these publications were included. *Table 1* shows the characteristics of the 12 papers included in the study. Six studies were prospective and the remainder were retrospective. The total number of patients in the included articles was 4218. Of these, 751 patients (17·8 (95 per cent confidence interval 16·7 to 19·0) per cent) had regional nodal metastasis in SLNBs. The proportion of tumour-positive sentinel lymph node dissections in included articles ranged from 12·5 to 24·6 per cent. Most studies used a combination of dye and γ probe techniques.

The SLNB-positive rates were compared with Breslow thicknesses, categorized by the previous version (1997) of the American Joint Committee on Cancer Melanoma Staging System. This showed that as the thickness of the primary tumour increased, the number of patients with a positive SLNB increased proportionally (*Table 2*).

χ^2 test for trend confirmed a strong positive correlation between tumour thickness and positive SLNB ($\chi^2 = 274.81$, 1 d.f., $P < 0.001$). Only two of the 12 studies contained any patients with tumour thickness less than 0·75 mm and a positive SLNB.

Discussion

An analysis of pooled data in this review demonstrated a positive correlation between Breslow thickness and SLNB positivity. This confirms the potential value of using Breslow thickness to select patients for SLNB.

In the group of patients with tumours thinner or equal to 0·75 mm the rate of positive biopsy was 1·0 per cent in the studies analysed; performing the biopsy in these patients therefore appears questionable, albeit based on a sample of only 199 patients. There is less certainty about tumours between 0·75 mm and 1·00 mm in thickness as this group still has a low risk of nodal involvement[26]. Although the majority of surgeons do not recommend SLNB for thin melanomas (less than 1 mm), advocating watchful waiting,

Table 1 Characteristics of included articles

Reference	Year	*n*	Proportion with positive SLNB according to tumour thickness*				Study type	Technique applied	SLNB-positive patients (%)†
			< 0·75 mm	0·76–1·50 mm	1·51–4·0 mm	> 4·0 mm			
Bachter *et al.*[14]	2001	248	0	0·07 (0·03)	0·22 (0·05)	0·44 (0·10)	R	γ probe in 176 patients, dye and γ probe in 80	13·3 (9·6, 18·1)
Caggiati *et al.*[15]	2000	202	0	0·05 (0·03)	0·23 (0·04)	0·50 (0·13)	R	Dye and γ probe	17·3 (12·7, 23·1)
Gennari *et al.*[16]	2000	133	0	0·02 (0·02)	0·32 (0·06)	0·47 (0·12)	P	Dye and γ probe	21·8 (15·6, 29·6)
Jansen *et al.*[17]	2000	195	0	0·08 (0·04)	0·23 (0·04)	0·53 (0·08)	P	Dye and γ probe	24·6 (19·1, 31·1)
Murray *et al.*[18]	2000	360	0	0·09 (0·03)	0·22 (0·03)	0·27 (0·06)	R	Mainly γ probe	17·5 (13·9, 21·8)
Rossi *et al.*[19]	2000	100	0	0·11 (0·06)	0·26 (0·07)	0·36 (0·09)	R	Dye and γ probe	23·0 (15·8, 32·2)
Muller *et al.*[20]	2000	203	0	0·15 (0·04)	0·26 (0·05)	0·57 (0·13)	P	Dye and γ probe	19·7 (14·8, 25·7)
Wagner *et al.*[21]	2000	264	0·03 (0·03)	0·11 (0·03)	0·20 (0·04)	0·42 (0·09)	R	Dye and γ probe	17·0 (13·0, 22·0)
Gershenwald *et al.*[22]	1999	565	0	0·05 (0·01)	0·19 (0·02)	0·34 (0·06)	R	Dye only in 196 patients; others dye and γ probe	15·0 (12·3, 18·2)
Haddad *et al.*[23]	1999	693	0	0·07 (0·02)	0·19 (0·02)	0·29 (0·05)	R	Mainly dye and γ probe	14·4 (12·0, 17·2)
Morton *et al.*[24]									
MSLT group	1999	551	0	0·11 (0·02)	0·23 (0·03)	0·28 (0·06)	P	Dye and γ probe	18·7 (15·7, 22·2)
JWCI group	1999	584	0	0·12 (0·02)	0·29 (0·03)	0·33 (0·05)	P	Dye and γ probe	22·6 (19·4, 26·2)
Krag *et al.*[25]	1995	120	0·04 (0·04)	0·03 (0·03)	0·22 (0·06)	0·27 (0·13)	P	γ probe	12·5 (7·7, 19·6)

Values in parentheses are *s.e. or †95 per cent confidence interval. P, prospective; R, retrospective; SLNB, sentinel lymph node biopsy; MSLT, multicentre selective lymphadenectomy trial; JWCI, John Wayne Cancer Institute

Table 2 Frequency of regional sentinel lymph node metastasis according to Breslow thickness (pooled data from included studies)

Tumour thickness (mm)	*n*	No. of SLNB-positive patients	Proportion (%)
≤ 0·75	199	2	1·0 (0·1, 3·6)
0·76–1·50	1600	133	8·3 (7·0, 9·8)
1·51–4·0	1904	433	22·7 (20·9, 24·6)
> 4·0	515	183	35·5 (31·4, 39·7)
Total	4218	751	17·8 (16·7, 19·0)

Values in parentheses are 95 per cent confidence intervals. SLNB, sentinel lymph node biopsy

there are data to indicate that performing SLNB in these patients might reasonably be considered when ulceration, lymphatic invasion or Clark level greater than 3 is present[12,27]. In summary, the current data support an international consensus that SLNB is inappropriate for patients with melanomas of Breslow thickness less than 1 mm. In the very rare instances in which such thin tumours have other adverse histological characteristics there may be some justification for choosing SLNB, although there are no clear data to support this view.

Patients with melanoma of Breslow thickness more than 1·0 mm and less than 1·5 mm have a low but definite risk of micrometastases. If the intention is to improve staging and on this basis to consider patients for trials of adjuvant therapies, it appears reasonable to carry out SLNB. However, biopsy has a relatively low positive rate in this group. In the absence of any evidence of an effect on outcome, it seems reasonable to make a decision about whether to proceed to SLNB in any individual patient based on the options for adjuvant therapy or the need for a better estimate of prognosis.

In patients with melanoma of Breslow thickness between 1·51 and 4·0 mm, the risk of a positive SLNB is significantly higher at 22·7 per cent. In this group biopsy seems appropriate and it represents an effective staging tool in relation to trials of adjuvant therapies. However, in the presence of additional poor prognostic markers, such as a high tumour mitotic rate, ulceration, regression, or even a truncal tumour in a male, it currently seems unreasonable to deny adjuvant therapy based on a SLNB result.

The value of SLNB for tumours of Breslow thickness greater than 4·0 mm is questionable because the risk of haematogenous spread is so high. However, some authors have recently suggested that additional prognostic information does come from SLNB in affected patients[28], and that negative biopsy is known to select some patients with an unexpectedly good prognosis[29].

Although SLNB is widely practised as a staging procedure, its sensitivity is less favourable than was previously assumed[30]. Not surprisingly, the indications for this diagnostic test, and its clinical reliability and usefulness, are still viewed as controversial and remain to be established. The effect of SLNB and subsequent lymphadenectomy on survival is currently being investigated and the results of randomized clinical trials are awaited. While SLNB has became a routine method for staging regional lymph nodes in the USA, in Australia and Europe it is not accepted as the standard of care at this time[31,32].

A detailed analysis of the correlation between known prognostic indicators (such as Breslow thickness, the presence of ulceration, Clark level, gender, site, age, and possibly even mitotic rate and the presence of a lymphocytic reaction) and SLNB positivity (and then outcome) should be carried out in ongoing SLNB trials. This will determine what additional prognostic information is afforded by SLNB over histology. Patients may then be properly selected for SLNB.

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Randomized clinical study of the prevention of pulmonary complications after thoracoabdominal resection by two different breathing techniques

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Background: Pulmonary complications are frequently seen after thoracoabdominal resection of the oesophagus. The aim of this study was to compare the effects of two different breathing exercise regimens applied in the immediate postoperative period on the risk of pulmonary insufficiency after thoracoabdominal resection.

Methods: Seventy patients undergoing thoracoabdominal resection for cancer of the oesophagus and cardia were randomized after operation to breathing exercises by inspiratory resistance–positive expiratory pressure (IR-PEP) ($n = 36$) or continuous positive airway pressure (CPAP) ($n = 34$). The study groups were well matched for all relevant clinical and demographic data.

Results: Respiratory function deteriorated significantly immediately after operation; the lowest values of forced vital capacity and peak expiratory flow were measured during the first postoperative day and oxygen saturation was lowest on days 4–6. Significantly fewer patients in the CPAP group required reintubation and prolonged artificial ventilation ($P < 0.05$). There were minor non-significant differences between the study groups with respect to respiratory and other postoperative variables, usually in favour of CPAP.

Conclusion: Provision of CPAP in the immediate postoperative period decreased the risk of respiratory distress requiring reintubation and the need for artificial ventilation compared with breathing exercises by IR-PEP.

Paper accepted 5 June 2002

British Journal of Surgery 2002, **89**, 1228–1234

Introduction

Upper abdominal surgery alters postoperative pulmonary function, as reflected by impairment in lung volumes accompanied by a decrease in arterial partial pressure of oxygen ($P\text{aO}_2$) as well as oxygen saturation[1–4]. Adding a thoracic incision to this operative procedure further accentuates this adverse sequence, and many reports have emphasized the high incidence of postoperative hypoxaemia, respiratory complications and distress following thoracoabdominal resection[5–7]. The complexity of a thoracoabdominal resection for carcinoma of the oesophagus or cardia is further enhanced by the development of atelectasis during anaesthesia, combined with postoperative diaphragmatic dysfunction[8–10]. In addition, the transposition of a hollow viscus, such as the stomach, into the chest may further restrict respiratory function[5].

Various breathing devices have been used after abdominal or thoracic surgery to improve postoperative pulmonary function[11,12]. To prevent these complications after upper abdominal surgery, controlled data have been presented to support the use of positive expiratory pressure (PEP), inspiratory resistance–positive expiratory pressure (IR-PEP) or continuous positive airway pressure (CPAP)[1,3,4]. When it comes to more extensive surgical procedures, such as thoracoabdominal resection, few studies have addressed the issue and the picture is far from clear. The aim of this study was to compare IR-PEP and CPAP, applied in the immediate postoperative period, on the risk of pulmonary insufficiency and need for reintubation and artificial ventilation after thoracoabdominal resection.

Patients and methods

Seventy patients undergoing thoracoabdominal resection, mainly for carcinoma of the oesophagus or cardia, were included in the trial to compare two different breathing exercises after thoracoabdominal oesophageal resection. The ethics committee of the university approved the study protocol, and informed consent was obtained from each patient before entry into the trial.

The demographic data of the patients are shown in *Table 1*. All patients with a malignant disease underwent computed tomography of the thorax and abdomen, and endoscopic ultrasonography to assess the tumour node metastasis status of the tumour. The majority of this group of patients also received preoperative radiochemotherapy. The total time required for the administration of neoadjuvant therapy was 5·5 weeks[13]. The operation was carried out 4–6 weeks after completion of radiochemotherapy.

During the week before surgery each patient underwent plain chest radiography and a bicycle exercise test during which an electrocardiogram was recorded continuously and the maximal physical performance was assessed.

During the day before surgery all patients received preoperative information from a specialized physiotherapist. This included a presentation on the breathing exercises used in the trial and the importance of early mobilization.

The following investigations were performed: oxygen saturation, forced vital capacity (FVC) and peak expiratory flow (PEF). These investigations were carried out with the patient in the sitting position using an oxymeter (Ohmeda 3700; Louisville, Colorado, USA), vitalograph (Wicatest 3; Mijnhardt, Odijk, The Netherlands) and a peak flow meter (Wright, London, UK). The best results of three valid assessments of FVC and PEF were compiled.

Antibiotics (metronidazole in combination with cefuroxime or cefotaxime) were given at induction of anaesthesia and continued postoperatively as long as the thoracic drains remained in place. All patients underwent thoracoabdominal operations with a midline abdominal incision and a right thoracotomy through the fifth intercostal space. In patients with cancer a two-field lymphadenectomy was carried out with one lung deflated during the posterior mediastinal lymph node dissection. All visceral conduits were drained by use of an indwelling nasogastric tube, which remained in place for at least 3 days.

Perioperative data are presented in *Table 2*. All patients were artificially ventilated with a positive end-expiratory

Table 1 Demographic data on patients allocated to inspiratory resistance–positive expiratory pressure or continuous positive airway pressure after thoracoabdominal resection

	IR-PEP (*n* = 36)	CPAP (*n* = 34)
Sex ratio (F : M)	5 : 31	5 : 29
Age (years)	64·1(9·7)	62·0(14·3)
Height (m)*	174·0(8·9)	175·0(7·8)
Weight (kg)*	71·0(14·8)	72·4(10·9)
Weight loss (%)*†	11·0(10·3)	14·4(12·6)
Preoperative haemoglobin*	121·7(18·0)	124·6(17·4)
Smoker		
Yes	15	12
No	9	8
Ex-smoker	12	14
Lung disease	6	5
Preoperative radiochemoherapy	18	19
Physical performance (W)*	125·6(43·6)	125·5(30·1)
ASA score		
1	0	0
2	25	18
3	11	16

*Values are mean(s.d.). †In relation to preoperative body-weight. IR-PEP, inspiratory resistance–positive expiratory pressure; CPAP, continuous positive airway pressure; ASA, American Society of Anesthesiologists. There were no significant differences between groups

Table 2 Tumour classification and perioperative data on patients undergoing thoracoabdominal surgery

	IR-PEP (*n* = 36)	CPAP (*n* = 34)
TNM classification		
T1	3	3
T2	5	5
T3	20	18
T4	2	4
N0	14	18
N1	16	12
M0	30	30
Benign disease	2	1
Missing data	4	3
Duration of anaesthesia (h)*	6·8(1·2)	6·8(1·2)
Duration of surgery (h)*	5·1(1·0)	5·2(0·9)
Type of reconstruction		
Colon	3	3
Jejunum	3	3
Gastric tube	30	28
Duration of lung deflation (min)*	77·8(35·9)	78·2(34·8)
Blood loss (ml)*	1050(745)	776(416)
Artificial ventilation in connection with surgery (h)*	29·6(9·9)	26·7(3·9)

*Values are mean(s.d.). IR-PEP, inspiratory resistance–positive expiratory pressure; CPAP, continuous positive airway pressure; TNM, tumour node metastasis. There were no significant differences between groups pressure of at least 5 cmH_2O overnight to reach an acceptable fraction of inspired oxygen (FiO_2) (35 per cent or less) before extubation and randomization. A computerized stratified randomization was carried out incorporating factors such as the American Society of Anesthesiologists score, working capacity, spirometry, sex, age, lung disease, smoking history, preoperative haemoglobin level, weight loss, preoperative radiochemotherapy, blood loss, surgical procedure and operative time. Thirty-six patients were allocated after operation to IR-PEP and 34 to CPAP. Two of the patients initially allocated and randomized were reintubated within less than an hour after extubation and therefore never tried the breathing exercises. One of the patients needed reoperation for postoperative bleeding and the other was found to have a bilateral vocal cord palsy that necessitated reintubation.

IR-PEP was carried out by deep breathing exercises with a PEP mask (PEP/respiratory muscle training set; Astra Tech, Mölndal, Sweden). This device comprises a T valve dividing inspiration and expiration. Resistances were applied on the whole breathing cycle using nipples with an inner diameter of 5·0 mm on the inspiration side and 2·5–3·0 mm on the expiration side, creating a pressure of -5 cmH_2O during inspiration and $+10$ cmH_2O during expiration. The exercises included 30 deep breaths with huffing and coughing between every tenth breath at 2-h intervals.

Patients randomized to CPAP received breathing exercises with the CPAP system in a Servo 300 (Siemens Elema, Solna, Sweden) during the first 3 days after operation in the intensive care unit (ICU). Optimal resistance was 5·0–10·0 cmH_2O, based on the acceptance and evaluation of the optimal ratio between tidal volume and breathing frequency for the individual patient. The treatment was given for 30 min every 2 h.

The surveillance of breathing exercises was similar in the IR-PEP and CPAP groups, and all patients stayed in the ICU for at least 3 days after extubation. In the surgical ward IR-PEP was used for all patients.

After 15 min without oxygen supplementation, arterial oxygen tension was measured with the patient in the sitting position once every day for the 3 days after operation and oxygen saturation was measured under similar conditions for the first 8 days. If saturation fell below 85 per cent, the 'air test' was interrupted. FVC and PEF were measured on days 1, 3, 6 and 8 with the patient in the sitting position under sufficient pain relief.

All patients had an epidural catheter inserted preoperatively at the mid-thoracic level for pain relief. Sufentanil 1 μg/ml was delivered continuously through this catheter with the addition of a local anaesthetic. The epidural infusion rate was individualized to reach efficient segmental analgesia of at least T4–10. All patients were given a daily dose of paracetamol 4 g rectally. Pain relief was assessed by use of a visual analogue scale (VAS) from 0 to 10; a pain score of less than 4 was considered acceptable. More than 90 per cent of all documented pain scores were 0 or 1 on the VAS.

The primary endpoint of this study was to decrease the need for reintubation and artificial ventilation. The criterion for upgrading the breathing regimens was defined as a PaO_2 of less than 10 kPa with a FiO_2 of 50 per cent on mask, at two consecutive blood gas analyses. In the IR-PEP group CPAP was first tried to alleviate respiratory distress and mechanical ventilation was not instituted until the patient failed with CPAP according to the above criterion. If failure according to the same criterion occurred in the CPAP group a longer period of CPAP was tried before the patient was intubated and ventilated mechanically.

In addition to respiratory parameters the following variables were recorded: rate and extent of mobilization, time to full mobilization, 30-day in-hospital mortality rate, postoperative care at the clinic and need for additional supportive care.

Statistical analysis

Differences between and within the groups were analysed by use of the Student's t test and χ^2 test. For an estimated difference of 30 per cent between the rates of reintubation in the groups, at a power of 80 per cent and a significance level of $P < 0.05$, it was calculated that each study group should incorporate 35 patients.

Results

The requirement for reintubation and prolonged artificial ventilation was significantly higher in patients allocated to postoperative IR-PEP (seven *versus* one) ($P < 0.05$). Two of the seven patients in this group who required reintubation died within 30 days of operation as did the patient in CPAP group. Although failure of treatment in the IR-PEP group was always followed by CPAP treatment before intubation and mechanical ventilation, only one patient in whom IR-PEP failed could manage with an extended CPAP regimen, while the other seven patients needed reintubation and artificial ventilation. In the CPAP group only one patient needed reintubation and artificial ventilation, while another patient managed with an extended respiratory regimen with longer periods of CPAP owing to early and extensive left lung atelectasis soon after extubation.

A significant decrease in the level of respiratory variables studied was seen in all patients (*Figs 1* and *2*). On average, FVC and PEF deteriorated to about 40 per cent of

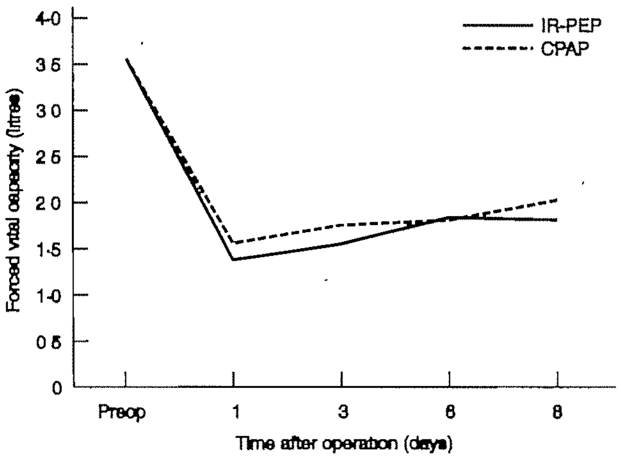

Fig. 1 Effect of thoracoabdominal resection on forced vital capacity in patients allocated to inspiratory resistance–positive expiratory pressure (IR-PEP) or continuous positive airway pressure (CPAP). Values are mean(s.d.). Preop., before operation

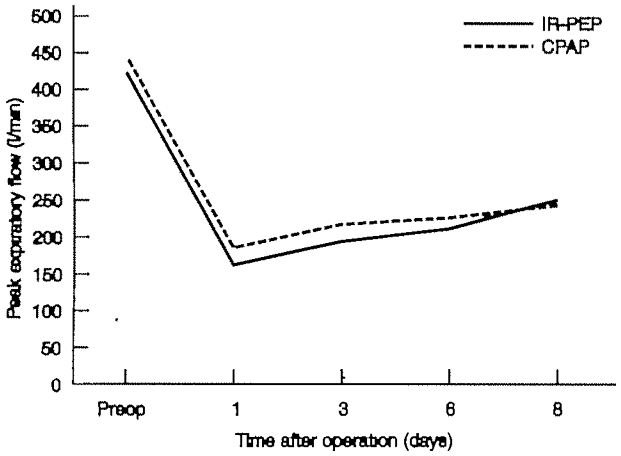

Fig. 2 Effect of thoracoabdominal resection on peak expiratory flow in patients allocated to inspiratory resistance–positive expiratory pressure (IR-PEP) or continuous positive airway pressure (CPAP). Values are mean(s.d.). Preop., before operation

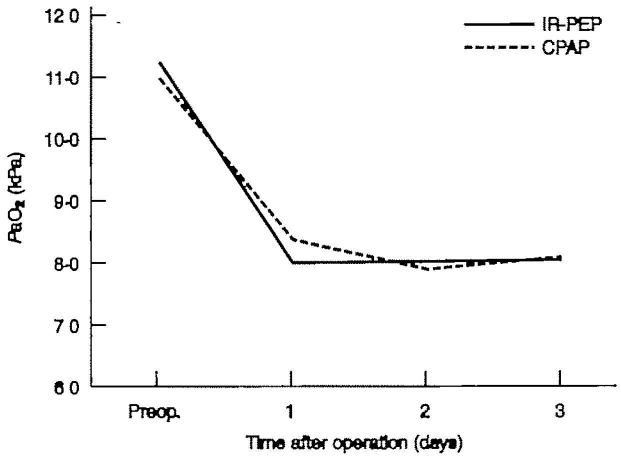

Fig. 3 Effect of thoracoabdominal resection on arterial partial pressure of oxygen (P_aO_2) in patients allocated to inspiratory resistance–positive expiratory pressure (IR-PEP) or continuous positive airway pressure (CPAP). Values are mean(s.d.). Preop., before operation

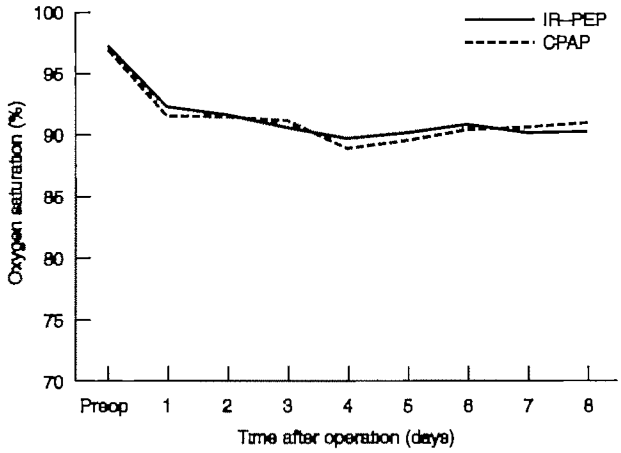

Fig. 4 Effect of thoracoabdominal resection on oxygen saturation in patients allocated to inspiratory resistance–positive expiratory pressure (IR-PEP) or continuous positive airway pressure (CPAP). Values are mean(s.d.). Preop., before operation

preoperative values. During the first week the recovery was slow and on the 8th day after operation FVC attained a level of about 60 per cent of that recorded before operation, while PEF remained at about 50 per cent. The arterial oxygen pressure and saturation followed a similar pattern (*Figs 3* and *4*); the lowest values in saturation were obtained during the 4th postoperative day and did not increase thereafter during the study period of 8 days. Despite the tendency to higher levels in some of these variables in the CPAP group no significant differences in these variables could be demonstrated between the two study groups.

There were no significant differences in clinical outcome between the CPAP and IR-PEP groups (*Table 3*). However, the clinical significance of an enhanced need for reintubation owing to respiratory distress was illustrated by the associated occurrence of multiple organ failure in six of the eight patients who required reintubation and ventilation.

Discussion

This randomized and controlled clinical study confirmed the previously documented substantial impairment in

Table 3 Postoperative course after thoracoabdominal resection in patients allocated to either inspiratory resistance–positive expiratory pressure or continuous positive airway pressure after thoracoabdominal resection

	IR-PEP (n = 36)	CPAP (n = 34)
Stay in ICU (days)*	5·8(5·0)	5·2(2·7)
Time to mobilization (days)*		
Walking in the room	3·4(1·3)	3·3(1·2)
Fully mobilized	6·0(1·4)	6·6(2·5)
Postoperative hospital stay (days)*	14·7(10·1)	12·2(5·8)
Convalescence care	30 of 32	30 of 33
Death within 30 days	4	1

*Values are mean(s.d.). IR-PEP, inspiratory resistance–positive expiratory pressure; CPAP, continuous positive airway pressure; ICU, intensive care unit. There were no significant differences between groups

respiratory function that follows thoracoabdominal surgical procedures[5–7]. The deterioration in respiratory function was reflected by the prolonged decline in oxygen saturation and spirometric variables. The lung volumes seemed to ameliorate somewhat from the lowest value reached during the first day after operation, while the oxygen saturation did not reach its lowest level until day 4 and did not increase thereafter during the 8 days of study. There were non-significant minimal numerical differences between the IR-PEP and CPAP groups in all these secondary endpoint variables. However, analysis of the primary endpoint, i.e. the requirement for reintubation and prolonged artificial ventilation, revealed a significant difference in favour of the CPAP group: only one patient required reintubation compared with seven patients in the IR-PEP group. Real differences in spirometric volumes and saturation (during air breathing) were not possible to calculate owing to lack of data in the most severely affected patients.

To understand the mechanisms that may be involved in respiratory deterioration after thoracoabdominal procedures it is important to analyse separately the impact on respiratory function of abdominal and thoracic incisions. After major abdominal surgery pulmonary function and respiratory gas exchange deteriorate. Postoperative hypoxaemia reaches its lowest value immediately after operation and usually continues for another 24–48 h[1,4]. After abdominal surgery the postoperative pulmonary complication rate varies between 4 and 80 per cent, a variability that depends on the definitions used[3]. Evidence in favour of physiotherapy in preventing complications is found in randomized clinical trials, which have shown that each method evaluated is better than no therapy[11,12]. In addition, PEP, IR-PEP and CPAP seem to offer advantages in terms of decreased incidence of postoperative pulmonary complications and increased functional residual capacity and oxygen saturation compared with incentive spirometry (IS) or ordinary deep breathing[11,12].

After transthoracic procedures, pulmonary complication rates after lung resection have been reported to vary between 5 and 60 per cent, again depending on the composition of the patients and criteria used[14–16]. There are few controlled trials describing the efficacy of various physiotherapeutic regimens after this type of surgery[14,16].

A combined thoracoabdominal incision elicits disturbances in respiratory function, which are of an entirely different magnitude to those produced by separate abdominal or thoracic ones. To this is added the consequences of a deflated lung, which is preferred by many surgeons to facilitate the dissection of the posterior mediastinum (as was the case in the present study). The positioning of the stomach within the thorax implies a particular restrictive respiratory change. Furthermore, the intrathoracically positioned stomach is open to atmospheric pressure and may vary in size with the latter with subsequent respiratory variations.

The rate of respiratory complications after oesophagogastric resection varies between series, from 8 to about 45 per cent[5–7,17,18]. Adequate postoperative management is critical to prevent these complications, and early extubation and epidural analgesia have been suggested to markedly decrease the pulmonary morbidity rate[19–21]. The present patients all underwent early mobilization and active physiotherapy to improve pulmonary function. The approach to extubation and analgesia was also standardized to facilitate the scientific evaluation of each intervention. Pain control was achieved in all patients by use of a segmental thoracic epidural analgesia, which has been shown to reduce the hypoxaemia and alveolar arterial oxygen difference compared with that in patients in whom analgesia was controlled with intravenous morphine after oesophagectomy[22].

There are no studies concerning the effectiveness of breathing exercises after thoracoabdominal oesophageal surgery. Gosselink *et al.*[14] have evaluated physiotherapy, including breathing exercises and huffing/coughing with or without IS, in patients undergoing oesophageal resection but by a thoracic incision only. No additional effect of IS was recorded. Both PEP and IS increase tidal volumes whereas FRC is only increased by PEP[23]. CPAP also increases FRC while tidal volumes remain small or normal. The modern concept for ventilator treatment in respiratory distress syndromes is to open up the lung with, and keep it open by, application of a high positive end-expiratory pressure, which is actually what CPAP does during spontaneous breathing[24]. Moreover, low tidal volumes are recommended for the treatment of acute respiratory distress syndrome to avoid overdistension of the lungs[25,26].

Patient compliance was high in this study. The PEP mask is simple, and easy to describe and to handle both for the patient and nursing staff. In the early postoperative period it may, however, be difficult for the patient to keep the mask close enough to the face to reach the preferred airway pressure and volumes. A low expiratory pressure is often seen among patients with low tidal volumes and low inspiratory as well as expiratory flow. The present patients decreased their FVC and PEF values to 40–50 per cent of the preoperative levels. To avoid this low pressure during the breathing exercises, the valve can be mounted on a mouthpiece. The CPAP system on the other hand does not need any cooperation from the patient. The high-flow CPAP maintains a high airway pressure during the whole breathing cycle whereby FRC expands. Depending on the flow rate, the use of CPAP may be associated with a risk of gastric distension and is therefore sometimes recommended for use only in selected patients. This was not a significant problem in the current study but the oesophageal conduit was decompressed by use of a nasogastric tube during the entire period of CPAP use.

In conclusion, postoperative pulmonary complications and respiratory deterioration remain significant problems after thoracoabdominal resection for carcinoma of the oesophagus and gastro-oesophageal junction. Postoperative physiotherapy including CPAP, instituted directly after extubation and maintained for the first 3 days followed by IR-PEP, significantly reduced the respiratory distress leading to reintubation and prolonged artificial ventilation compared with IR-PEP only.

Acknowledgements

Sources of financial support were Renée Eander, LSR memory, Royal and Hvitfeldtska and Vårdal foundations, and LUA project of Sahlgrenska University Hospital (S02711).

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Original article

Laparoscopic ultrasonography is a complement to cholangiography for the detection of choledocholithiasis at laparoscopic cholecystectomy

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Background: Intraoperative cholangiography and laparoscopic ultrasonography are both used in the detection of common bile duct stones at laparoscopic cholecystectomy. The aim of this prospective study was to determine whether laparoscopic ultrasonography has an alternative or a complementary role with respect to cholangiography in achieving this end.

Methods: The biliary trees of 900 patients undergoing laparoscopic cholecystectomy were examined routinely by the two methods. The diagnostic power of each investigation and of the two techniques in combination was evaluated. The statistical non-random concordance between the two methods was also determined.

Results: Laparoscopic ultrasonography was performed in all 900 patients. Cholangiography was performed in 762 (85 per cent). The mean (range) duration was 9·8 (4–21) min for laparoscopic ultrasonography and 17·6 (7–42) min for cholangiography. For the detection of common bile duct stones, with a kappa coefficient of 0·57 (95 per cent confidence interval (c.i.) 0·43 to 0·71), the non-random concordance between the two methods was considered to be fair to good. The sensitivity of laparoscopic ultrasonography was 0·80 (95 per cent c.i. 0·65 to 0·91) and its specificity was 0·99 (95 per cent c.i. 0·98 to 1·00). The respective values for cholangiography were 0·75 (95 per cent c.i. 0·59 to 0·87) and 0·99 (95 per cent c.i. 0·98 to 1·00). The examinations combined had a sensitivity of 0·95 (95 per cent c.i. 0·86 to 0·99) and a specificity of 0·98 (95 per cent c.i. 0·96 to 1·00).

Conclusion: Laparoscopic ultrasonography and intraoperative cholangiography are complementary, as the combination of both methods maximizes the intraoperative detection of choledocholithiasis.

Paper accepted 9 May 2002

British Journal of Surgery 2002, 89, 1235–1239

Introduction

Choledocholithiasis occurs in up to 15 per cent of patients with symptomatic cholelithiasis[1]. The advent of laparoscopic cholecystectomy has enlivened the debate between those who defend systematic intraoperative opacification of the common bile duct (CBD)[2,3] and those who advocate a selective approach[4]. Intraoperative cholangiography (IOC) is a tool for the detection of CBD stones, as well as for the detection of variants in biliary anatomy. To this end, IOC is performed routinely by many surgeons despite the fact that false-positive and false-negative results are not uncommon[2].

The availability of B-mode real-time ultrasound machines, combined with purpose-designed transducers, has led to renewed interest in intraoperative ultrasonography for the detection of choledocholithiasis[5–12]. In a preliminary study[13] the authors reported that, while laparoscopic ultrasonography (LU) detected anomalies of biliary anatomy in only half as many laparoscopic cholecystectomies as cholangiography, it achieved comparable results in terms of sensitivity for the detection of choledocholithiasis. Tranter *et al.*[14] recently proposed LU as an alternative to cholangiography for the detection of CBD stones at laparoscopic cholecystectomy. They did not envisage, like the present[13] and other[5–12] authors, that the two methods could be seen as complementary. The aim of this prospective study was to determine whether LU represents an alternative or a complement to cholangiography for the detection of choledocholithiasis at laparoscopic cholecystectomy.

Patients and methods

Patients

Between November 1994 and September 2000, the biliary trees of 900 patients undergoing laparoscopic cholecystectomy were routinely visualized by both LU and IOC. The study population consisted of 641 women and 259 men with a mean age of 52 (range 18–95) years and a mean weight of 72 (range 44–153) kg. Indications for operation were biliary colic (563 patients), acute cholecystitis (254), cholangitis (44) and gallstone pancreatitis (39). General fitness was assessed by the American Society of Anesthesiologists (ASA) score: 328 patients were classified as ASA I, 430 as ASA II and 142 as ASA III. Patients classified as ASA IV were excluded from the study, as this was considered to be a relative contraindication to laparoscopy. All patients had undergone abdominal ultrasonography with measurement of CBD calibre (greater than 8 mm in 108 patients), serum bilirubin (greater than 26 μmol/l in 85 patients), serum alkaline phosphatase (greater than 200 units/l in 134 patients) and serum amylase (greater than 200 units/l in 70 patients). Endoscopic retrograde cholangiography was performed in 32 patients initially referred for jaundice or cholangitis. In ten of these, the CBD was clear. In 22, stones were detected and extracted after endoscopic sphincterotomy.

Methods

LU and IOC were performed routinely. The laparoscopic ultrasound transducer (Brüel and Kjaer, Naerum, Denmark) was introduced via the umbilical port with the camera in the 10-mm left upper quadrant port. It was passed under vision over the capsule of the liver. The gallbladder was then viewed through the liver parenchyma (segment 5). The confluence of the right and left hepatic ducts was seen through segment 4. The transducer was then placed over the anterolateral aspect of the hepatic pedicle. Once the bile duct had been identified, the transducer was passed along its length from top to bottom. When the duodenum was reached, the ampulla of Vater and distal CBD were examined. Any intraductal calculi were sought. The total time taken for the sonographic examination was noted.

Calot's triangle was then dissected. On transversely incising the cystic duct, a ureteric catheter was passed, and a cholangiogram performed after injection of iodinated contrast medium. The cholangiography films were interpreted immediately by a radiologist who was unaware of the findings of the ultrasound examination. The presence of any stones was documented and the time taken for the procedure recorded.

Patients were reviewed at 1, 6 and 12 months after surgery.

Statistical analysis

The diagnostic power of each investigation was evaluated by the following statistical measures: sensitivity, specificity, positive predictive value and negative predictive value[15]. These calculations were made using a contingency table that cross-tabulated the results of each technique with those of the gold standard. The latter consisted of surgical confirmation of the presence or absence of CBD stones or, where LU and IOC were negative, of the absence of retained stones based on clinical and biochemical criteria after 1 year of follow-up. The same statistical indices were calculated similarly for the two techniques in combination. For this it was assumed that LU and IOC were independent of each other, based on the fact that the surgeon abided by the blinded radiologist's report on the IOC when deciding whether to explore the CBD. In other words, knowing the result of one test did not influence that of the other. Results were calculated on an intention-to-perform basis. To determine the statistical non-random concordance between the two methods, the kappa coefficient was computed. This was considered fair to good with a coefficient between 0·41 and 0·80, and excellent for a coefficient of 0·81–1·0[16]. The 95 per cent confidence interval was calculated for all indices. These precise computations were made by using the exact formula of the binomial distribution. Statistical analysis was performed using SPSS® (SPSS, Chicago, Illinois, USA) and StatXact® (Cytel Software Corporation, Cambridge, Massachusetts, USA) software.

Results

All 900 patients underwent LU. IOC was not achieved in 138 patients (15 per cent); this was due to failed cystic duct cannulation in 119 patients, because of a narrow lumen or cystic duct valves in 49 patients and an excessively inflamed cystic duct in 70 patients with acute cholecystitis. For the remaining 19, iodine allergy was a contraindication to cholangiography. The mean duration of LU was 9·8 (range 4–21) min and that of IOC was 17·6 (range 7–42) min.

CBD exploration was undertaken in 78 patients in whom at least one of the two investigations suggested filling defects. Sixty of these investigations confirmed the presence of stones (7 per cent of the series), whereas 18 did not (2 per cent). Forty-one cases of choledocholithiasis were dealt with laparoscopically; nine required conversion to an open procedure and ten were treated by postoperative endoscopic stone extraction. No patient was lost to follow-up at 1 month, 18 (2 per cent) at 6 months and 45 (5 per cent) at 1 year. During the 12-month follow-up period, no patient presented with clinical or biochemical evidence of retained CBD stones.

Hyperechoic lesions were detected by ultrasonography in 54 patients, of which 48 were true positives and six false positives (calculi lodged in the cystic duct). IOC similarly showed 57 filling defects, of which 45 were true positives and 12 false positives. The latter were defects suggested in at least one of the films taken for each patient and subsequently judged to be air bubbles when radiologists and surgeons later jointly reviewed the cholangiograms. There were 12 false negatives for LU (due to non-visualization of the distal CBD) and 15 for IOC (because of poor-quality films). The false negatives for one investigation were nevertheless detected as true positives by the other. No false negatives were noted in cases where both investigations concurred with a negative result. The non-random concordance between the two methods, with a kappa coefficient of 0·57 (95 per cent confidence interval 0·43 to 0·71), was considered to be fair to good according to Fermanian[16] (*Table 1*).

Table 1 Non-random concordance between laparoscopic ultrasonography and intraoperative cholangiography for the detection of common bile duct stones

	Intraoperative cholangiography	
	Negative results	Positive results
Laparoscopic ultrasonography		
Negative results	822	24
Positive results	21	33

κ = 0·57 (95 per cent confidence interval 0·43 to 0·71), P < 0·001

Where IOC was not successful, LU diagnosed 134 true negatives and four true positives. This was confirmed by operative CBD exploration in the latter group and subsequent clinical follow-up in the former group. It should also be noted that LU revealed microbubbles of gas in the CBD of ten of the 22 patients who had undergone preoperative endoscopic retrograde cholangiography with sphincterotomy and stone extraction. Although these were considered an artefact, they did not result in any false negatives or false positives, as such bubbles are not hyperechoic and do not produce shadow cones.

As the results were calculated on an intention-to-perform basis, calculations were done with a denominator of 900 cases for LU, IOC and the methods in combination. As shown in *Table 2*, the sensitivity was 0·80 and 0·75 for LU and IOC respectively. The specificity was 0·99 for each method. When the two methods were considered in combination, the sensitivity was 0·95 and specificity 0·98. In summary, by supplementing IOC with LU, an additional 15 true positives were detected at the expense of declaring an additional six false positives.

Discussion

IOC has traditionally been used for the detection of choledocholithiasis during open and laparoscopic cholecystectomy. Its other benefit is in the definition of biliary anatomy, permitting the detection of anomalies[13] and possible protection against bile duct injury[17]. Other authors such as Wright and Wellwood[18] have suggested that IOC is not a prerequisite for the safe performance of laparoscopic cholecystectomy and cannot be relied upon to prevent biliary injuries. IOC is contraindicated in pregnancy and iodine allergy. It is difficult to perform in acute cholecystitis when the cystic duct lumen is narrow or when cannulation is prevented by cystic duct valves. Although the authors sought to undertake it routinely, this was not possible on 138 occasions (15 per cent of patients in the study). The failure rate reported in the literature for unselected cases is generally less than 15 per cent[19].

Table 2 Quantitative evaluation of the diagnostic techniques: laparoscopic ultrasonography, intraoperative cholangiography and the combination of both methods

Performance measure	Laparoscopic ultrasonography	Intraoperative cholangiography	Combination of both methods
Sensitivity	0·80 (0·65, 0·91)	0·75 (0·59, 0·87)	0·95 (0·86, 0·99)
Specificity	0·99 (0·98, 1·00)	0·99 (0·98, 1·00)	0·98 (0·96, 1·00)
Positive predictive value	0·89 (0·74, 0·97)	0·79 (0·63, 0·90)	0·77 (0·61, 0·90)
Negative predictive value	0·99 (0·98, 1·00)	0·98 (0·96, 0·99)	0·99 (0·98, 1·00)

Values in parentheses are 95 per cent confidence intervals

Studies on the use of intraoperative ultrasonography in conventional surgery have shown it to be comparable to cholangiography for the detection of choledocholithiasis[20, 21]. LU requires special training, preferably supervised by a sonographer experienced in both conventional and laparoscopic intraoperative ultrasonography[13]. In this series, a trained operator could perform full biliary LU in less than 10 min, as shown by others[5,6,8]. There is no restriction on the type of case in which LU can be used, and it can always be performed even where IOC has failed.

In this study, the non-random concordance between the two methods for the detection of CBD stones was fair to good, but not excellent. It has been suggested previously[5, 6,8,11,13] that the results of the two methods are equivalent in terms of sensitivity, but the non-random concordance between them has not been calculated. The complementary nature of the two methods, or their use in combination for the intraoperative detection of CBD stones, has also been suggested, but not formally reported.

There were no false negatives in cases where both investigations concurred with a negative result. Positivity in one of the investigations was considered an indication for CBD exploration, thus yielding 60 true positives (7 per cent of the series) but also 18 in which the CBD was found to be free of stones (2 per cent). These should not necessarily be seen as needless explorations of the CBD but as the acceptable price of ensuring 95 per cent sensitivity and 98 per cent specificity when the two methods are used in combination. The time taken to perform the examinations (10 min for LU and 15–20 min for IOC) cannot be seen as excessive as the combination optimizes the chances of detecting choledocholithiasis intraoperatively. Subsequent laparoscopic treatment of choledocholithiasis as part of the same procedure can lead to a shorter hospital stay[22].

In conclusion, LU can be performed in cases were IOC has failed or is contraindicated. The non-random concordance between LU and IOC for the detection of CBD stones is considered to be fair to good. With a sensitivity of 95 per cent, which is clearly superior to that of LU and IOC taken separately, the combination of the two investigations maximizes intraoperative detection of choledocholithiasis and should be recommended. LU and cholangiography can therefore be seen as complementing rather than competing with each other.

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Original article

Size of lesion is not a criterion for resection during management of giant liver haemangioma

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Background: The unknown natural history and risk of complications of large haemangiomas may pose therapeutic dilemmas. The authors describe their experience with the management of giant haemangiomas.

Methods: Patients with a giant haemangioma were identified by a survey of the hospital database. Forty-nine patients with a haemangioma of at least 4 cm in diameter presented between January 1990 and December 2000. Medical records were analysed retrospectively.

Results: Eleven patients had surgical treatment and 38 were managed conservatively. The median diameter of the tumours was 8·0 cm in surgically treated patients and 6·0 cm in the group managed by observation. Surgery-related morbidity occurred in three patients, and abdominal complaints persisted in three of ten patients with a symptomatic lesion. During a median follow-up of 52 months, 12 non-operated patients had mild abdominal complaints, considered to be unrelated to the lesion. In these patients symptoms either diminished or became minimal during follow-up. Complications did not occur.

Conclusion: Observation of giant haemangiomas can be performed safely. The authors advocate resection of cavernous liver haemangiomas only in patients with persistent severe symptoms.

Paper accepted 13 June 2002

British Journal of Surgery 2002, **89**, 1240–1244

Introduction

Cavernous haemangioma is the most common benign tumour of the liver, with an estimated prevalence of 5–7 per cent[1]. The incidental finding of liver haemangioma has increased considerably as many patients undergo modern imaging techniques[2,3]. Although most of these lesions remain asymptomatic, they may be responsible for pain due to capsular stretch, partial infarction or pressure on surrounding tissues. More rarely, haemangiomas may rupture, or be associated with a consumptive coagulopathy (Kasabach–Merritt syndrome) or abscess formation[4–7]. Strategies for the management of liver haemangioma have ranged from selective observation to a variety of radiological and surgical interventions[8–12]. While there is general agreement that small asymptomatic lesions should be managed conservatively, the unknown natural history and the possibility of complications of larger, or giant, haemangiomas (4 cm or more) makes treatment selection difficult[3,9].

The management of large haemangiomas has become increasingly conservative with time. Because serious complications may occur during conservative management of liver haemangiomas, a retrospective review was undertaken to identify the magnitude of these risks.

Patients and methods

A survey of the hospital database was performed to identify all consecutive patients with a diagnosis of giant haemangioma (at least 4 cm in diameter) who presented at University Hospital Rotterdam-Dijkzigt between January 1990 and December 2000. Forty-nine patients were identified. The diameter of the tumour was 10 cm or more in eight patients. Liver haemangiomas were solitary in

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Tumour characteristics

	Surgery (*n* = 11)	Observation (*n* = 38)
Location		
Right	4	22
Left	5	6
Bilateral	2	10
No. of tumours		
One	9	22
Two	2	8
Three or more	0	8
Diameter (cm)		
Mean	9·5	6·5
Median	8·0	6·0
Range	4·0–20·0	4·0–25·0

31 of the 49 patients. Bilateral giant haemangiomas were found in 12 patients (*Table 1*).

There were 33 women (67 per cent) and 16 men, with a mean age of 55 (range 32–89) years. Eleven (22 per cent) of the 49 patients underwent operation and 38 (78 per cent) were managed by observation. The medical records of all patients were reviewed to document clinical presentation, diagnostic strategies, treatment, complications and follow-up.

Diagnostic investigation included ultrasonography, triphasic spiral computed tomography (CT) and magnetic resonance imaging (MRI). The current MRI protocol for haemangiomas includes T2-weighted images with short and long echo times, multiphasic dynamic contrast-enhanced T1-weighted images, and delayed fat-saturated dynamic contrast-enhanced T1-weighted images. In the first part of this retrospective study, ultrasonographically guided needle cytology or biopsy was performed when there was still doubt regarding the diagnosis after the use of imaging modalities and a conservative approach was being considered. The histological diagnosis of cavernous liver haemangioma was retained if the biopsy specimen demonstrated endothelium-lined spaces containing either fibrin thrombi or aggregates of red blood cells separated from one another by connective tissue septa. More recently, fine-needle aspiration cytology or biopsy has been performed only when MRI is not conclusive.

A variety of surgical procedures were employed (*Table 2*), designed to minimize the unnecessary loss of normal liver tissue. When feasible, enucleation was preferred. In patients with multiple haemangiomas, resection was performed for the tumour that was presumed to be causing symptoms, considering size and localization.

Follow-up after either surgical or conservative treatment consisted of physical examination and ultrasonographic visualization of the liver.

Table 2 Surgical procedures undertaken in 11 patients

	n	Diameter (cm)
Right hemihepatectomy	2	7·0, 12·0 (9·5)
Right extended hemihepatectomy	1	20·0
Left hemihepatectomy	2	9·0, 12·0 (10·5)
Segmental resection	3	4·0, 7·0, 9·0 (6·7)
Enucleation	3	5·0, 6·0, 7·0 (6·0)

Values in parentheses are mean

Table 3 Clinical presentation of 49 patients with a giant haemangioma

	Surgery (*n* = 11)	Observation (*n* = 38)	Total (*n* = 49)
Abdominal complaints	10	12	22 (45)
Incidental finding	1	22	23 (47)
Suspected metastasis	—	3	3 (6)
Raised γ-glutamyl transferase level	—	1	1 (1)

Values in parentheses are percentages

Results

In 27 (55 per cent) of the 49 patients, haemangioma was an incidental finding during abdominal imaging for unrelated pathology or during follow-up or staging of an extrahepatic malignancy (*Table 3*). Symptoms potentially related to haemangioma included upper abdominal pain, fullness and dyspepsia.

Liver function test results were abnormal in 25 patients (51 per cent) but did not contribute to the diagnosis. No patient had thrombocytopenia or anaemia.

Ultrasonography was performed in all 49 patients and demonstrated haemangioma in 30. Twenty-three patients had CT, which was conclusive in 21 patients. In some of the patients with a typical lesion, MRI was performed additionally to increase the level of confidence and experience with this imaging technique. In eight of nine patients MRI established the diagnosis unequivocally. When fine-needle cytology or biopsy was employed, haemangioma was detected in five of ten and in nine of 11 patients respectively.

Surgical treatment

In ten patients an operation was performed where abdominal symptoms were considered to be related to haemangioma (infarction, capsular stretch or pressure on surrounding tissues). One patient underwent operation for an asymptomatic giant haemangioma (diameter 12 cm) with persistent growth (5 cm during radiological follow-up of 36 months). The mean greatest diameter of all resected tumours was 9·5 (median 8·0, range 4·0–20·0) cm (*Table 1*).

Postoperative complications occurred in three patients. One patient developed secondary bleeding that necessitated relaparotomy; one had a pleural effusion and another had a subhepatic abscess, both of which required drainage. During postoperative follow-up of 24·5 (range 13–110) months, abdominal symptoms persisted in three patients. Two of these symptomatic patients had bilateral haemangiomas at the time of operation. They have been managed conservatively by radiological follow-up of the contralateral lesions, which have been left *in situ* (6 and 7 cm). There was no surgery-related mortality.

Conservative management

Thirty-eight patients were managed conservatively. Twelve non-operated patients had mild abdominal pain or discomfort, considered to be unrelated to the lesion *(Table 3)*. The mean greatest diameter of the tumour in these symptomatic patients (6·1 (median 6·0, range 4·0–11·0) cm) was not significantly different from that in the symptomatic patients who underwent surgery (mean 9·7 cm, median 8·5 cm) ($P = 0{\cdot}36$).

During a mean follow-up of 59 (median 52, range 12–122) months, symptoms had either diminished or become minimal in all 12 patients with abdominal complaints. None of the patients who were asymptomatic at the time of first referral developed abdominal pain. In 32 patients the tumour was followed by means of ultrasonography. An increased diameter was observed in only one patient with an asymptomatic haemangioma. Coagulation disorders, other complications or tumour-related death have not occurred.

Discussion

In patients with benign liver tumours, surgery may relieve complaints in a large proportion of those with symptoms. In a substantial proportion of patients (15–30 per cent), however, symptoms persist after resection probably as a consequence of another undiagnosed problem, such as irritable bowel syndrome, peptic ulcer or reflux disease[8,13]. It is essential to decide whether the mass is indeed the cause of the patient's complaints, as simple observation of a benign liver lesion might be the best clinical approach without the risks of surgery and the potential for symptom resolution. In patients with a haemangioma, it may be even more difficult to correlate symptoms with size and location. Indications for operation have traditionally been the presence of symptoms, the development of complications, and the need to establish a definite diagnosis when radiological and histological studies were inconclusive. Liver haemangiomas have also been resected because of a perceived risk of spontaneous or traumatic rupture, and the possibility of the Kasabach–Merritt syndrome, a consumption coagulopathy with low platelet counts and hypofibrinogenaemia[6,9,14,15]. The potential for complications of a liver haemangioma is minimal[4,16] and does not justify, *per se*, resection of all haemangiomas. The risk of significant and sometimes uncontrollable intraoperative bleeding of hypervascular lesions, in addition to the common risks of any liver resection[17–19], should be carefully balanced against the benefit that might be expected from surgery. The reported mortality rate associated with elective liver resection of such tumours ranges from 0 to 4 per cent[8,13,20,21]. The latter figure must be considered unacceptable, taking into account the benign nature and high prevalence of the tumour.

Specific features of cavernous liver haemangioma may be apparent with a variety of imaging techniques such as ultrasonography, dynamic contrast-enhanced CT and MRI. With ultrasonography, a typical haemangioma is characterized as a sharply marginated, lobulated, predominantly hyperechoic lesion[22–24]. Haemangiomas may be complicated by bleeding, scar tissue or calcification[24]. Such lesions have a variable appearance at ultrasonography. In addition, the ultrasonographic appearance of uncomplicated haemangiomas may overlap with those of primary or secondary malignant liver tumours. In patients with an unclear diagnosis and in those with a known (colorectal) malignancy or cirrhosis, the authors recommend MRI because of its high specificity in the diagnosis of haemangioma. At MRI, haemangiomas are typically very bright on T2-weighted images (*Fig. 1*) and show peripheral nodular enhancement on dynamic contrast-enhanced T1-weighted images (*Fig. 2*). Occasionally, small haemangiomas may show a homogeneous intense enhancement during early phases of the dynamic study, although haemangiomas, unlike malignant lesions, retain contrast material and stay hyperintense on delayed contrast-enhanced imaging[22,24]. The overall accuracy of MRI for the detection and characterization of haemangiomas has been reported to be high, with a specificity of 90–100 per cent and a sensitivity of about 90 per cent[22–26], especially when T2-weighted images with short and long echo times are combined with multiphasic dynamic contrast-enhanced images, and delayed contrast-enhanced images. The results of MRI in the present study, although obtained in only a small number of patients with haemangioma, are in accordance with those reported previously[22,24]. The use of other invasive imaging methods, such as scintigraphy and technetium-99m-

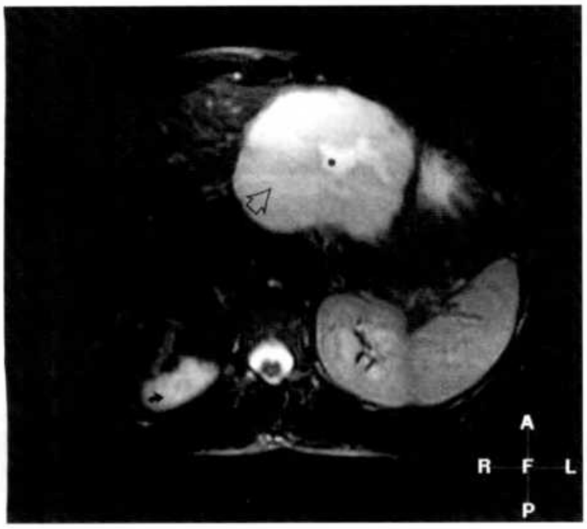

Fig. 1 T2-weighted magnetic resonance image with fat saturation showing a typical giant haemangioma (arrowhead) with a central scar (*) on the left side of the liver, and a small haemangioma in the right liver (black arrow). Both lesions are sharply marginated and very bright compared with surrounding liver

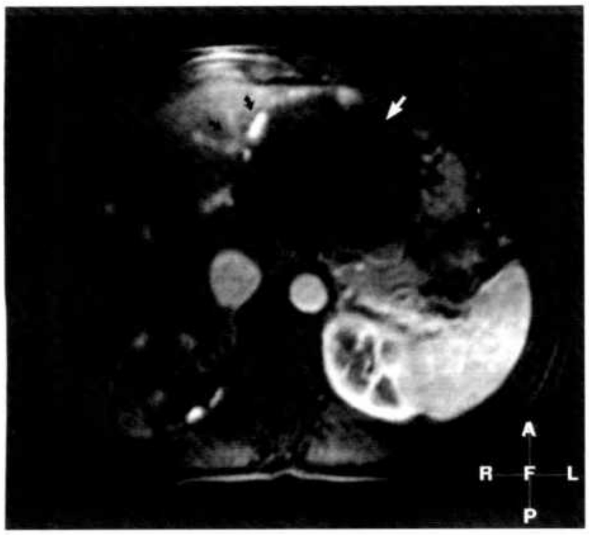

Fig. 2 T1-weighted image during the arterial phase of a dynamic study after intravenous injection of magnetic resonance imaging contrast medium (gadolinium–diethylenetriamine penta-acetate), showing typical peripheral nodular enhancement (black arrows) in both lesions (giant haemangioma indicated with white arrow). The presence of a combination of a bright lesion on a T2-weighted image and peripheral nodular enhancement is pathognomic for liver haemangioma

labelled red blood cell scanning, has also been reported for the diagnosis of benign liver lesions and especially haemangiomas[25,26].

The risk of needle-induced bleeding during ultrasonographically or CT-guided biopsy in benign hypervascular tumours is reported to be low (0·03–0·04 per cent)[27,28]. In the present series there were no complications following biopsy. A tissue diagnosis is recommended when the radiological diagnosis remains unclear and conservative treatment is being considered.

Conservative management of liver haemangioma is preferred because of the minimal risk of complications. As supported by the present observation, mild symptoms often resolve spontaneously during follow-up, and operation is not completely successful in terms of symptomatic relief. In addition, this series derives from a tertiary referral centre with a higher proportion of large tumours than is observed in the general population. The study clearly demonstrates that a confident diagnosis may be made using modern recent high-resolution radiological studies, and that conservative management can be undertaken safely. Based on the present experience, surgery for liver haemangioma is advocated only in patients with incapacitating symptoms. The size of the lesion is not a criterion for resection and some exceptional indications or complications which may necessitate liver surgery or even transplantation[12,13,29] confirm the importance of this general guideline for the treatment of liver haemangioma: observe the lesion, unless the patient has severe symptoms.

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Original article

Morbidity and mortality associated with pancreatogastrostomy and pancreatojejunostomy following partial pancreatoduodenectomy

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Background: The pancreatic anastomosis is still the Achilles heel in partial pancreatoduodenectomy (PPD).
Methods: This study describes retrospectively a series of 441 patients who underwent standard or extended PPD and reconstruction by either pancreatogastrostomy or pancreatojejunostomy over a period of 13 years (1988–2000).
Results: Reconstruction of the pancreatic remnant was achieved by pancreatogastrostomy in 250 patients (56·7 per cent) and by pancreatojejunostomy in 191 patients (43·3 per cent). The leakage rate of the pancreatic anastomosis was 2·8 per cent after pancreatogastrostomy *versus* 12·6 per cent after pancreatojejunostomy ($P < 0{\cdot}001$), whereas other surgical complications (bile leakage, haemorrhage, pancreatitis) were identical in the two groups. The leakage rate after standard PPD with or without vascular reconstruction was 2·0 per cent (four of 205 patients) after pancreatogastrostomy and 11·5 per cent (18 of 156) after pancreatojejunostomy ($P < 0{\cdot}001$); following extended PPD it was 6·7 per cent (three of 45) after pancreatogastrostomy and 17·1 per cent (six of 35) after pancreatojejunostomy. The mortality rate due to leakage was 1·6 per cent (four of 250 patients) after pancreatogastrostomy *versus* 5·2 per cent (ten of 191) after pancreatojejunostomy ($P = 0{\cdot}037$).
Conclusion: Pancreatogastrostomy is a safe and reliable method of reconstruction after PPD that may be associated with a lower leakage and mortality rate than pancreatojejunostomy.

Paper accepted 11 June 2002

British Journal of Surgery 2002, 89, 1245–1251

Introduction

Continuous improvements in surgical techniques and growing experience have led to marked reductions in the complication rate after partial pancreatoduodenectomy (PPD) over the past two decades. Perioperative mortality rates after standard PPD are often below 5 per cent, although morbidity remains high with rates of around 20–40 per cent[1–5]. In spite of these improvements the pancreatic anastomosis remains the Achilles heel of the operation. The most severe complication is leakage of the pancreatic anastomosis, which can lead to severe pancreatitis, bleeding from adjacent large vessels, peritonitis and/or sepsis.

Various methods for reconstruction after PPD have been described. With regard to the pancreatic anastomosis, reconstruction is basically possible by two different techniques, with drainage into either a jejunal loop (pancreatojejunostomy) or the remaining stomach (pancreatogastrostomy). Occlusion of the pancreatic stump without an anastomosis is usually considered only in cases of small atrophic pancreas. In most centres reconstruction involves an anastomosis between the jejunum and the entire end of the resected pancreas with or without a duct-to-mucosa anastomosis. Pancreatogastrostomy was first used clinically in the 1940s[6]; although it has been adopted by several groups[7–10], it has never achieved broad acceptance.

This retrospective analysis describes experience with pancreatogastrostomy for reconstruction after PPD in a single centre over a 13-year interval. During this period either pancreatojejunostomy or pancreatogastrostomy was

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

used depending on the preference of the surgeon. Postoperative morbidity and mortality were assessed with specific attention to pancreatic leakage after both types of reconstruction.

Patients and methods

Patients, indications and extent of resection

The study included all 441 patients who underwent PPD at the Klinik für Viszeral- und Transplantationschirurgie of the Medizinische Hochschule Hannover between January 1988 and December 2000. Five patients without anastomosis of the pancreatic remnant were not included. Patients who were treated by duodenum-preserving pancreatic head resection or with segmental resection of the pancreas were excluded because reconstruction in these patients was always done by pancreatojejunostomy.

The indications for PPD were pancreatic head or ampullary cancer in 260 patients (59·0 per cent) (pancreatogastrostomy, 58·0 per cent; pancreatojejunostomy, 60·2 per cent), chronic pancreatitis in 66 patients (15·0 per cent) (pancreatogastrostomy, 14·0 per cent; pancreatojejunostomy, 16·2 per cent), endocrine tumours in 29 (6·6 per cent) (pancreatogastrostomy, 6·8 per cent; pancreatojejunostomy, 6·3 per cent), and papillary adenoma or cystadenoma in 20 (4·5 per cent) (pancreatogastrostomy, 5·6 per cent; pancreatojejunostomy, 3·1 per cent). In 19 patients (4·3 per cent) PPD was performed as part of a more extended resection of advanced cholangiocarcinoma or gallbladder cancer. Other indications existed in 47 patients (10·7 per cent) (pancreatogastrostomy, 9·6 per cent; pancreatojejunostomy, 12·0 per cent), such as peripancreatic metastases of colonic or renal cell cancer, or emergency operation. The mean(s.d.) age of all patients was 56·5(13·0) years (pancreatogastrostomy, 56·8(13·1) (range 17–87) years; pancreatojejunostomy, 56·3(12·8) (range 11–89) years).

In 361 cases (81·9 per cent) an isolated PPD was performed (pancreatogastrostomy, 82·0 per cent; pancreatojejunostomy, 81·7 per cent), with or without vascular resection ('standard PPD'); 80 patients (18·1 per cent) had additional major organ resections (e.g. liver or colonic resection) ('extended PPD') (pancreatogastrostomy, 18·0 per cent; pancreatojejunostomy, 18·3 per cent). Patients who underwent incidental appendicectomy or small (subsegmental) liver excision were included in the 'standard PPD' group. In nine cases (2·0 per cent) the operation was performed on an emergency basis, for example in cases of acute bleeding, trauma, or severe necrotizing head pancreatitis and duodenal perforation after endoscopic retrograde cholangiopancreatography.

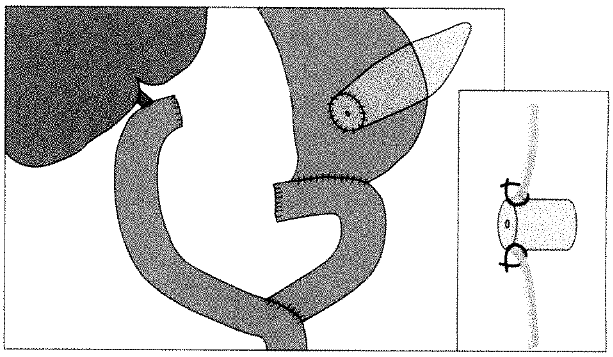
The extent of gastric resection was not standardized. There was, however, a tendency towards a limited antrectomy. In about 10 per cent of operations a pylorus-preserving procedure was performed.

Perioperative somatostatin was used only sporadically, in less than 10 per cent of patients.

Techniques of pancreatic anastomosis

For reconstruction by pancreatogastrostomy, the pancreatic remnant was mobilized for about 1–2 cm from the resection surface. The back wall of the body of the stomach was opened by a 2–3-cm gastrotomy. The pancreas was sutured to the stomach by a single row of inverting interrupted sutures (generally 4/0 polydioxanone), starting with the anterior wall of the aspect of the pancreas and leading to a telescope-type anastomosis (*Fig. 1a*). Before finishing the gastrojejunal anastomosis, a gastric tube was placed in the distal stomach opposite to the pancreatogastrostomy site.

Reconstruction by pancreatojejunostomy also required mobilization of the pancreas for about 1–2 cm from the


a Pancreatogastrostomy

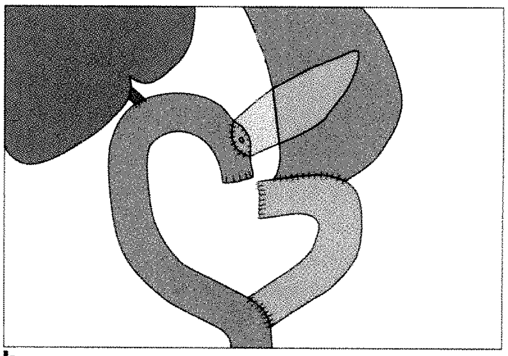

b Pancreatojejunostomy

Fig. 1 Reconstruction of the pancreatic remnant after partial pancreatoduodenectomy. **a** Pancreatogastrostomy (insert depicts anastomosis of whole pancreas into posterior gastric wall). **b** Pancreatojejunostomy

resection surface. Anastomosis was then performed to a retrocolic Roux-en-Y loop with an end-to-side technique. Again the anastomosis was performed between the tissue of the pancreas using an inverting suture technique and interrupted polydioxanone sutures (*Fig. 1b*). Reconstruction of the bile duct was done end-to-side to the same Roux-en-Y loop some centimetres distal to the pancreatic anastomosis. In some of the patients having pancreatojejunostomy, the jejunal loop to the pancreas and bile duct was stented by placing either a gastric tube or an endobronchial suction tube in the bowel opposite to the pancreatic anastomosis, and exteriorizing this catheter 30–40 cm distally by fixing the jejunum at the anterior abdominal wall ('endoluminal stenting'). Selection of the method of reconstruction depended on the personal preference of the surgeon.

Data collection and analysis

Data collection was performed retrospectively using operation records, patient files and discharge letters. This included all major surgical complications, particularly those requiring surgical or interventional treatment. Prolonged but asymptomatic secretion of amylase-rich fluid from an intra-abdominal drain placed during operation was not documented systematically. Leakage of the pancreatic anastomosis as well as bile leakage was defined by clinical signs and symptoms (abdominal pain, signs of infection, or sepsis) with or without macroscopically recognizable secretion of the respective fluid (bile, pancreatic juice) from a drain. Thus, only findings that required an intervention were included. In patients who underwent reoperation, leakage was confirmed during operation, and in one patient it was documented after death.

Statistical analysis with performed with the χ^2 test, using Microsoft® Excel 2000 software (Microsoft®, Unterschleissheim, Germany).

Results

Types of reconstruction after partial pancreatoduodenectomy

Reconstruction was by pancreatogastrostomy in 250 (56·7 per cent) of the 441 patients, 205 after standard PPD and 45 after extended PPD. In 191 patients (43·3 per cent) reconstruction was by pancreatojejunostomy, 156 after standard PPD and 35 after extended PPD. In 57 cases of pancreatojejunostomy (12·9 per cent) additional external endoluminal stenting was performed.

Postoperative complications and overall mortality

Following pancreatogastrostomy, significant intra-abdominal complications were observed in 30 (12·0 per cent) of 250 patients, compared with 41 (21·5 per cent) of 191 patients after pancreatojejunostomy. Leakage of the pancreatic anastomosis occurred in seven patients (2·8 per cent) after pancreatogastrostomy, compared with 24 (12·6 per cent) after pancreatojejunostomy ($P < 0{\cdot}001$). After pancreatojejunostomy, no difference in leakage rate could be observed in patients with and without endoluminal stenting of the Roux-en-Y loop (nine (15·8 per cent) of 57 patients with stenting *versus* 15 (11·1 per cent) of 134 patients with no stenting). The frequency of haemorrhage requiring reoperation (3·2 *versus* 3·6 per cent), bile leakage (3·2 *versus* 3·1 per cent), pancreatitis without leakage (2·0 *versus* 1·6 per cent) and necrosis of the pancreatic remnant without primary leakage (0·8 *versus* 1·0 per cent) was similar after pancreatogastrostomy and pancreatojejunostomy (*Fig. 2*).

The postoperative in-hospital mortality rate for all patients was 7·9 per cent. Eleven patients (4·4 per cent) died after pancreatogastrostomy, compared with 24 (12·6 per cent) after pancreatojejunostomy ($P = 0{\cdot}002$). Leakage and mortality rates were lower for pancreatogastrostomy than for pancreatojejunostomy, for both standard and extended PPD (*Table 1*).

The overall rate of surgical complications was 38·5 per cent for 'experienced' surgeons *versus* 19·4 per cent for 'inexperienced' surgeons (personal experience of ten or fewer PPDs). The use of pancreatogastrostomy was the same in both groups (57·1 *versus* 53·4 per cent). Pancreas-related complications occurred in a total of 26 (7·6 per cent)

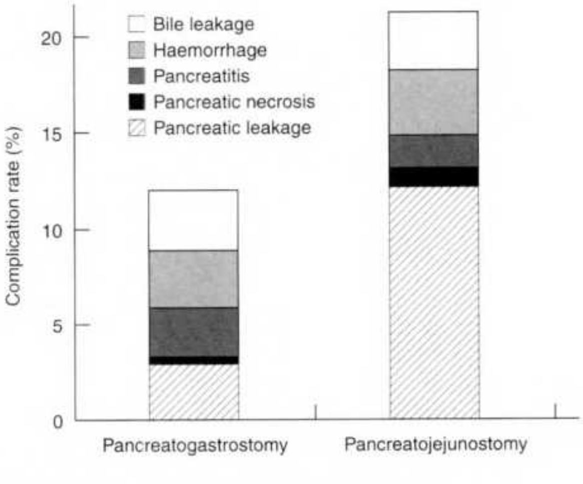


Fig. 2 Major surgical complications after partial pancreatoduodenectomy in relation to type of reconstruction

Table 1 Incidence of pancreatic leak and overall mortality in relation to type of reconstruction and extent of operation

	Pancreatic leakage		Overall mortality
	No. with leak	No. who died	
All patients			
PG (n = 250)	7 (2·8)	4 (1·6)	11 (4·4)
PJ (n = 191)	24 (12·6)	10 (5·2)	24 (12·6)
P*	< 0·001	0·037	0·002
Standard PPD†			
PG (n = 205)	4 (2·0)	2 (1·0)	7 (3·4)
PJ (n = 156)	18 (11·5)	5 (3·2)	10 (6·4)
P*	< 0·001	0·13	0·18
Extended PPD‡			
PG (n = 45)	3 (6·7)	2 (4·4)	4 (8·9)
PJ (n = 35)	6 (17·1)	5 (14·3)	14 (40·0)
P*	0·14	0·12	0·001

Values in parentheses are percentages. PG, pancreatogastrostomy; PJ, pancreatojejunostomy; PPD, partial pancreatoduodenectomy. †PPD with or without vascular reconstruction, and without other major organ resection; ‡PPD combined with other major organ resection (e.g. liver resection, colonic resection). *χ^2 test

of 343 patients operated on by experienced surgeons (seven (3·6 per cent) of 196 for pancreatogastrostomy *versus* 19 (12·9 per cent) of 147 having pancreatojejunostomy; P = 0·001), compared with four (4·1 per cent) of 98 patients operated on by inexperienced surgeons (one (1·9 per cent) of 54 for pancreatogastrostomy *versus* three (6·7 per cent) of 44 for pancreatojejunostomy; P = 0·201).

Management and outcome of pancreas-associated complications

The most relevant clinical complication related to the pancreatic remnant was leakage of the pancreatic anastomosis, which was observed in 31 patients. In two cases leakage was associated with complete necrosis of the pancreatic remnant. In a further three patients leakage resulted in severe bleeding due to the erosion of a major arterial vessel. Necrosis of the remaining pancreas without leakage (four patients) and endoluminal bleeding at the site of the pancreatic anastomosis (six patients) also occurred.

Management of clinically symptomatic pancreatic leakage was surgical in 29 patients; in one patient computed tomography-guided drainage was performed and in one leakage was diagnosed only after death. Completion pancreatectomy was performed in ten of 29 reoperated patients, eight of whom died. In 16 patients a localized leak was oversewn (n = 8) or a new anastomosis performed (n = 8) using the available Roux-en-Y loop (n = 3) or by conversion (pancreatogastrostomy to pancreatojejunostomy in one patient, pancreatojejunostomy to pancreatogastrostomy in four patients). One of these patients subsequently required completion pancreatectomy. Five of these 16 patients died. In a further three patients the anastomosis was taken down and the pancreatic remnant oversewn or drained externally; two of these three patients died. Altogether 16 of 31 patients with clinically relevant leakage of the pancreatic anastomosis died. After standard PPD the cause of death was directly or indirectly related to consequences of the pancreatic leakage in two (1·0 per cent) of the 205 patients following pancreatogastrostomy and in five (3·2 per cent) of 156 patients after pancreatojejunostomy (*Table 1*).

All four patients suffering from pancreatic necrosis without leakage had a completion pancreatectomy, with a fatal outcome in two. In the six patients with bleeding into the stomach or Roux loop, bleeding stopped with conservative treatment in two patients; in four, reoperation was performed and the bleeding point oversewn via an anterior gastrotomy or after opening the pancreatojejunostomy. All six patients survived.

Discussion

This retrospective study compared the results of pancreatogastrostomy in a series of 250 patients seen in a single centre over a period of 13 years with those of 191 patients reconstructed by pancreatojejunostomy following PPD. An identical rate of various surgical complications (haemorrhage, bile leak and pancreatitis) was seen with both methods, but the pancreatic leakage rate was lower after pancreatogastrostomy. Leakage occurred in about 12 per cent of cases after pancreatojejunostomy, compared with less than 3 per cent after pancreatogastrostomy. This lower rate of pancreatic leakage is in keeping with the majority of published reports, although these were all based on much smaller patient numbers[11–20] (*Table 2*). A literature review published by Mason[21] in 1999 reported an average rate of 4·7 per cent among 614 cases from studies published between 1990 and 1997. Studies that have compared pancreatogastrostomy and pancreatojejunostomy (generally on a retrospective basis or with historical controls) describe leak rates for pancreatojejunostomy of between 11·5 and 19·4 per cent[12,14,15,18,19]. The only randomized prospective study comparing both types of reconstruction reported a similar rate of pancreatic leakage for both methods of around 11–12 per cent[14]. The definition of pancreatic leak in that study was very broad and included cases of prolonged amylase-containing secretion through intra-abdominally placed drains without clinical symptoms.

Symptomatic leakage of the pancreatic anastomosis is a severe complication associated with a high mortality rate[22].

Table 2 Literature review of recently published major studies on pancreatogastrostomy

			Pancreatogastrostomy			Pancreatojejunostomy			
Reference	Location	Year	*n*	Leakage (%)	Mortality rate (%)	*n*	Leakage (%)	Mortality rate (%)	Type of study
Delcore *et al.*[11]	Kansas City	1990	45	0	2	—	—	—	Retrospective
Miyagawa *et al.*[12]	Shinshu	1992	32	3·1	0	31	19·4	6·0	Retrospective
Takao *et al.*[13]	Kagoshima	1993	46	2·0	4·0	—	—	—	Retrospective
Yeo *et al.*[14]	Baltimore	1995	73	12·3	NS	72	11·1	NS	Prospective randomized
Kim *et al.*[15]	Seoul	1997	48	2·1	4·2	38	15·8	7·9	Retrospective
Kapur *et al.*[16]	New Delhi	1998	125	0	4·8	—	—	—	Retrospective
Fabre *et al.*[17]	Montpellier	1998	160	2·5	3·0	—	—	—	Retrospective
Arnaud *et al.*[18]	Angers	1999	80	3·7	3·7	91	13·0	12·0	Prospective non-randomized
Takano *et al.*[19]	Tokyo	2000	73	0	0	69	13·0	12·0	Prospective non-randomized
O'Neil *et al.*[20]	Loyola	2001	102	8·8	3·9	—	—	—	Retrospective
Mason[21]	(Review)	1999	614	4·7	3·3	—	—	—	Retrospective

NS, not specified

Therefore it was not surprising to see that the lower leakage rate after pancreatogastrostomy was also associated with a reduction in the mortality rate of more than 50 per cent. In the present series, the mortality rate for pancreatogastrostomy after exclusion of patients with additional major organ resection was 3·4 per cent. Differences in mortality for the two types of reconstruction have been noted elsewhere (*Table 2*), with hospital death rates of around 4 per cent after pancreatogastrostomy *versus* 7–8 per cent after pancreatojejunostomy[12,15,18,19].

Some studies have shown that stenting may reduce the risk of leakage in patients having pancreatojejunostomy[23,24]. Failure to demonstrate this in the present series may have been due to suboptimal positioning of the stents inside the bowel, or to the use of stents that may have been occluded by mucosal folds or detritus. Selective cannulation of the pancreatic duct with direct stenting of the anastomosis might be more efficient in diverting this fluid. In contrast to standard reconstruction by pancreatojejunostomy, reconstruction by pancreatogastrostomy divides the flow of pancreatic juice and bile. The pancreas secretes into the stomach, which represents a large reservoir that is additionally decompressed by a gastric tube during the early postoperative phase. Thus, there is almost no risk of internal pressure on the pancreatic anastomosis after pancreatogastrostomy. An alternative option is the use of separate jejunal loops for reconstruction of the bile duct and pancreas.

Mortality rates due to pancreatic leak after PPD are frequently between 10 and 40 per cent[3,25,26]. The high overall mortality rate (16 of 31) for patients with pancreatic leakage in this series may be explained by two factors. A large proportion of patients underwent extended resection, which is associated with additional risks. Mortality after leakage was particularly high in this subgroup, although overall mortality was still lower for patients having pancreatogastrostomy than for those having pancreatojejunostomy. The definition of leakage included only clinical complications that required intervention. This is in contrast to other reports which have also included asymptomatic patients with prolonged drainage of amylase-rich fluid[14,26,27]. The very high mortality rate (eight of ten patients) following completion pancreatectomy is also in contrast to the findings of other publications[25], but again may reflect the number of extended operations. Therefore, prevention of pancreatic leakage must be a primary goal of the initial operation. This is of particular concern in patients with a soft (non-congested and non-fibrotic) pancreas, which carries an increased risk of leakage[26,28].

A number of factors influence interpretation of the presented data: the analysis is retrospective, the patient group was heterogeneous, and a large number of surgeons was involved. A large prospective randomized study to control for these factors would be difficult to conduct. In this respect, the large number of surgeons involved in the present series, as well as the heterogeneity of the patient group, reflects everyday practice. The fact that complication rates were higher for experienced surgeons than for less experienced ones (with a similar use of pancreatojejunostomy and pancreatogastrostomy in both groups) suggests that pancreas-related complications were not necessarily due to inadequate technical skill of the operating surgeon. The data even suggest that pancreatogastrostomy may be safe in the hands of less experienced surgeons (leakage rate less than 2 per cent).

Pancreatogastrostomy is a safe and reliable method for reconstruction of the pancreatic remnant following PPD. It appears to carry a lower risk of symptomatic pancreatic leakage and lower postoperative mortality than pancreatojejunostomy. Leakage still occurred in some patients, and further approaches to improve the safety of PPD should be considered. Stenting and transient external diversion of the pancreatic duct might be a way to secure the anastomosis in both pancreatojejunostomy and pancreatogastrostomy[24,29], particularly in patients with a 'soft' pancreas. Whether the perioperative use of octreotide can reduce the risk of pancreatic complications during PPD remains to be clarified, although some studies have suggested this[30]. The importance of the location of the anastomosis and the extent of gastric resection with pancreatogastrostomy is also not clear in clinical practice, although these factors have been cited as important in experimental studies[31,32]. Questions also remain regarding long-term endocrine and exocrine function after pancreatogastrostomy, and also quality of life. Available data from small series suggest that endocrine function appears to be similar after pancreatogastrostomy and pancreatojejunostomy, but exocrine function may be worse after pancreatogastrostomy[33-39]. These issues merit further examination.

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Original article

In situ ablation of experimental liver metastases delays and reduces residual intrahepatic tumour growth and peritoneal tumour spread compared with hepatic resection

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Background: The aim of this study was to evaluate the influence of *in situ* ablation and hepatic resection of experimental liver metastases on residual intrahepatic tumour growth and macroscopic peritoneal tumour spread.
Methods: Two colonic carcinomas (CC 531) were implanted into 90 WAG rat livers, one in the right liver lobe (untreated tumour) and one in the left liver lobe (treated tumour) of each rat. The animals were randomized into two test groups and a sham-operated control group. Animals in group 1 received *in situ* ablation (laser-induced thermotherapy) of the treated tumour. Rats in group 2 were submitted to partial hepatectomy. Untreated tumour volumes were calculated and the incidence of macroscopic peritoneal spread was determined at different times.
Results: After 21 days median (95 per cent confidence interval) volumes of untreated tumours were 507 (282) mm^3 in group 1, 2096 (994) mm^3 in group 2 and 1896 (755) mm^3 in group 3. Compared with values obtained before treatment, growth of the untreated tumours had increased significantly after 4 days in group 2, after 7 days in group 3 and after 10 days in group 1. Macroscopic peritoneal tumour spread was detected in six of 30 animals in group 1 (laser), in 20 of 30 in group 2, and in 24 of 30 in group 3.
Conclusion: Compared with hepatic resection, *in situ* ablation of experimental liver metastases delays and reduces residual intrahepatic tumour growth and macroscopic peritoneal tumour spread.

Paper accepted 5 June 2002

British Journal of Surgery 2002, **89**, 1252–1259

Introduction

Hepatic resection is the only curative treatment for colorectal liver metastases[1,2]. A 5-year survival rate of up to 38 per cent is achieved when prognostically relevant factors are considered. The most important clinical problem is that 30–50 per cent of patients develop intrahepatic recurrence despite curative resection[3–7]. This may be caused by pre-existing micrometastases at the time of the R0 resection, which lead to new macrometastatic spread[8]. It is unclear whether hepatic resection itself stimulates the growth of micrometastases. The fact that almost 80 per cent of intrahepatic recurrences occur in the first 2 years after operation suggests that the doubling time of colorectal liver metastases after resection is markedly shorter than has been assumed[9]. Experimental animal data also show that metastatic growth after liver resection is significantly accelerated in the course of hepatic regeneration[10–13].

As alternatives to hepatic resection, so-called *in situ* thermal ablation techniques, such as cryotherapy[14], radiofrequency therapy[15] and laser-induced thermotherapy (LITT)[16–19], are becoming of increasing interest in the treatment of liver metastases. In contrast to hepatic resection, they are minimally invasive, parenchyma preserving and repeatedly applicable. The aim of this study was to examine the growth of residual intrahepatic and metastatic extrahepatic tumour tissue after *in situ* ablation in comparison with hepatic resection.

Materials and methods

Animals and tumour model

Ninety male WAG rats with a body-weight of 200–280 g were used in the study. Animals were kept separately during the experiment with 12 h of light per day. They were fed a standard laboratory diet and provided with tap water. Maintenance and care of all experimental animals was carried out according to the guidelines of the responsible Animal Protection Commission and with the permission of the Senat für Gesundheit, Berlin (National Institute of Health for Use of Laboratory Animals). The tumour cell line CC 531 was obtained from the Deutsches Krebs Forschungszentrum, Heidelberg, Germany.

Intrahepatic tumour inoculation was performed with a tumour suspension produced *in vitro*. Tumour cells were cultivated and the tumour suspension was prepared as described previously[20]. For tumour implantation, the animals underwent laparotomy through a midline abdominal incision under general anaesthesia with ketamine (Ketanest®; Parke-Davis, Freiburg, Germany) 5 mg/100 g body-weight and xylazine (Rompun®; Bayer, Leverkusen, Germany) 0·3 mg/100 g body-weight. Two liver tumours were induced in all animals by a subcapsular injection of 10^6 tumour cells (0·1 ml tumour cell suspension) under the capsule of the anterior surface of the lateral left (treated tumour) and right (untreated tumour) superior liver lobe. Puncture sites were closed with acrylic glue to avoid tumour cell leakage into the peritoneal cavity.

Seven days after tumour inoculation, the animals underwent a further laparotomy as described above. The liver was shifted forward on to sterile gauze compresses. The largest width (A) and the maximum tumour diameters perpendicular to the width (B and C) were measured with a micrometer.

Laser and thermocouples

Laser was applied using a neodymium yttrium–aluminium–garnet laser (Medilas 2®; MBB-Medizintechnik, Munich, Germany) with a wavelength of 1064 nm. The laser light was delivered in the continuous-wave mode through a 400-μm fibre, which had a diffuser tip applicator (outer diameter 0·8 mm, active length 5·0 mm) at its distal end. The technical details of this applicator have been described elsewhere[21]. For complete tumour destruction, LITT was performed at a power setting of 2 W for 800 s, corresponding to a total energy output of 1600 J. To monitor the temperature during LITT, two nickel–chrome–nickel thermocouples (Standard Integrated Thermocouple Thermocoax®; Phillips, Hamburg, Germany) with a diameter of 0·6 mm were placed intrahepatically at the macroscopic tumour margin of both the treated and the untreated tumour. The temperature was measured continuously during and for 5 min after LITT. After treatment the diffuser tip applicator and the thermocouple were removed from all animals.

Liver resection

Partial hepatectomy (75 per cent) included removal of the left lateral (containing the treated tumour), median and caudate posterior lobes. After opening the abdomen, the liver was mobilized and resected using electrocautery and standard techniques as described elsewhere[22].

Experimental protocol

Animals were randomized into three groups. Only the tumour in the left lateral liver lobe was treated in groups 1 and 2. The tumour in the right superior lobe remained untreated in all cases. Animals in group 1 (laser; $n = 30$) were treated by LITT and those in group 2 (resection; $n = 30$) underwent partial hepatectomy as described above. In group 3 animals (control; $n = 30$) sham operation was performed exactly as in the resected animals except that the liver was only manipulated and not removed, leaving both tumours untreated. After treatment the abdomen was closed and the animals were kept under standard conditions.

Five animals from each group were killed 24, 48, 96 h, 7, 10 and 21 days after treatment. The animals were injected with 5-bromo-2′-deoxyuridine (BrdU; 200 mg/kg body-weight) in the tail vein 6 h before death. After complete hepatectomy, the greatest width (A) and the maximum diameters perpendicular to the width (B and C) of the untreated tumours were measured, and tumour volumes were calculated as described below. In addition, the entire intestine was removed from the peritoneal cavity and all tissue containing suspected tumour growth was preserved. The incidence of macroscopic peritoneal tumour spread was verified by further histological staining.

Tissue sectioning

The livers were completely sectioned into multiple slices. Adjacent tissue slices were divided into two parts, and one part of each sample was fixed in 0·9 per cent saline solution, frozen and stored at −80°C until use. The other part was fixed in 4 per cent formalin and embedded in paraffin to obtain sections for conventional histological examination (haematoxylin and eosin staining).

Apoptosis and tumour cell proliferation

The TUNEL method (terminal deoxyribonucleotidyl transferase-mediated deoxyuridine 5′-triphosphate (dUTP) nick end labelling) was used to investigate apoptosis. Apoptotic cells were detected on 5-μm cryostat sections using an apoptosis detection kit purchased from R&D Systems (Wiesbaden-Nordenstadt, Germany).

Before labelling, the sections were rehydrated and washed twice in phosphate-buffered saline (PBS). The labelling procedure involved permeabilization with CytoPore® (Amsterdam Biosciences, Freiburg, Germany) and blocking of endogenous peroxidase using 0·3 per cent hydrogen peroxide. After immersion in terminal deoxynucleotidyl transferase enzyme (TdT) labelling buffer for 5 min, the samples were covered with labelling reaction mixture and incubated for 1 h at 37°C. After blocking with TdT stop buffer and washing twice with PBS, detection was performed using streptavidin–horseradish peroxidase and diaminobenzidine working solution. Sections were counterstained using 1 per cent methyl green. Cryostat sections of 5 μm were used for immunohistochemical detection of BrdU. Staining was performed using the 5-bromo-2′-deoxyuridine Labeling Kit II® (Boehringer-LaRoche, Mannheim, Germany) as described previously[20].

In group 2 animals, remission of the laser-treated tumour was determined when no vital tumour cells could be detected in the haematoxylin and eosin-stained sections by light microscopy and immunohistochemical detection of BrdU was negative after *in vivo* incorporation. The TUNEL and BrdU tests were evaluated semiquantitatively; three representative areas per section were assessed under 400 × magnification. The expression was comprehensively rated as absent (–), slight (+), moderate (+ +) or strong (+ + +) for time-points from 24 h to 21 days.

Statistical analysis

Tumour volume (v) was calculated using the formula $v = 4\pi\ a\ b\ c/3$, in which a, b and c are the radii of the measured axes A, B and C described above.

Preinterventional tumour volumes were symmetrically distributed, so mean(s.e.m.) values were calculated. As a symmetrical distribution could not be assumed for post-interventional tumour volumes, median values with 95 per cent confidence intervals (c.i.) were determined. Non-parametric tests (Kruskal–Wallis) were used to calculate differences between the untreated tumours in groups 1 (laser), 2 (resection) and 3 (control) at the time-points from 24 h to 21 days. $P < 0{\cdot}05$ was considered statistically significant. To determine tumour growth the third root of untreated tumour volumes were formed, which were designated as the relative radius (relative radius (mm) = tumour volume $((\mathrm{mm}^3)^{1/3})$. According to this, the increase in relative radius could be assessed by calculating the difference in the relative radius before and after treatment. The median (95 per cent c.i.) values for each calculation were compared with a single-factor analysis of variance (Dunnett test, Scheffe test). $P < 0{\cdot}05$ was considered statistically significant.

Results

Temperature measurements

Increasing the laser energy applied in the course of LITT caused the temperature in group 1 to rise continuously at the treated tumour margin. In contrast, the temperature at the untreated tumour margin remained constant at the initial value throughout laser application in all cases. The temperature courses of the treated and untreated tumours in group 1 are presented in *Fig. 1*.

Tumour growth and remission of treated tumours

Before the intervention, the mean(s.e.m.) volume of the treated tumours in groups 1 (laser therapy), 2 (resection) and 3 (control) was 78·8(5·0), 81·0(4·1) and 89·6(3·9) mm³ respectively, with no significant differences between the groups. In group 1, complete thermocoagulation of the treated tumour was achieved in all cases. Histological examination of sections at the time of death showed no vital tumour cells after haematoxylin and eosin staining, and the immunohistological examination revealed negative BrdU tumour cell expression. In group 2, complete resection of the treated tumour was achieved in all cases. Histologically, the resection plane was tumour-free (R0 resection). In the control group, the treated tumour demonstrated macroscopic and microscopic vital tumour growth at all time-points.

Tumour volume and growth of untreated tumours

The mean(s.e.m.) volume of untreated tumours before the intervention in groups 1 (laser), 2 (resection) and 3 (control) was 80·0(4·4), 78·1(4·1) and 80·3(3·7) mm³ respectively,

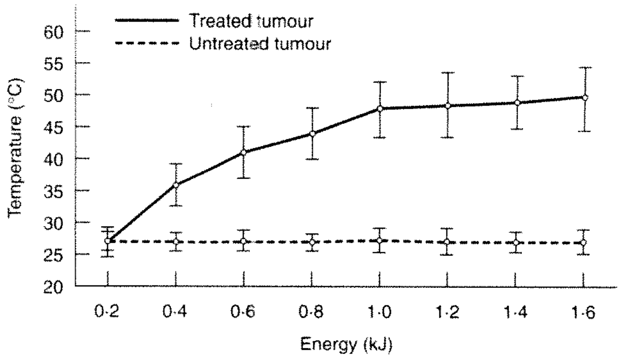

Fig. 1 Temperature course during laser-induced thermotherapy at the tumour margin of treated and untreated tumours in group 1 ($n = 30$). Values are mean(s.e.m.)

with no significant differences between the groups. At 96 h after the intervention, the median (95 per cent c.i.) tumour volume in group 1 (77 (20·8) mm^3) was smaller than that in group 2 (314 (101·5) mm^3; $P < 0{\cdot}009$) and group 3 (170 (62·3) mm^3; $P < 0{\cdot}004$). At 7 days after the treatment, the median (95 per cent c.i.) tumour volume in group 1 was smaller than that in group 3 (77 (97·8) *versus* 377 (146·7) mm^3; $P < 0{\cdot}006$), whereas the volume in group 2 (704 (171·0) mm^3) was greater than that in group 3 ($P < 0{\cdot}03$). Ten days after treatment, tumour volume in group 1 (339 (90·7) mm^3) was smaller than that in group 2 (1414 (40·1) mm^3) and group 3 (1026 (376·0) mm^3) (both $P < 0{\cdot}009$). Volumes of untreated tumours in groups 1–3 are given as median (95 per cent c.i.) in *Fig. 2*.

Fig. 3 shows representative gross sections of untreated tumours in the three groups at 24 h to 21 days after treatment. The calculated relative radii at 24 h to 21 days are given as median (95 per cent c.i.) in *Fig. 4*. At 24 and 48 h after treatment, the untreated tumours in groups 1–3 showed no significant increase in relative radius compared

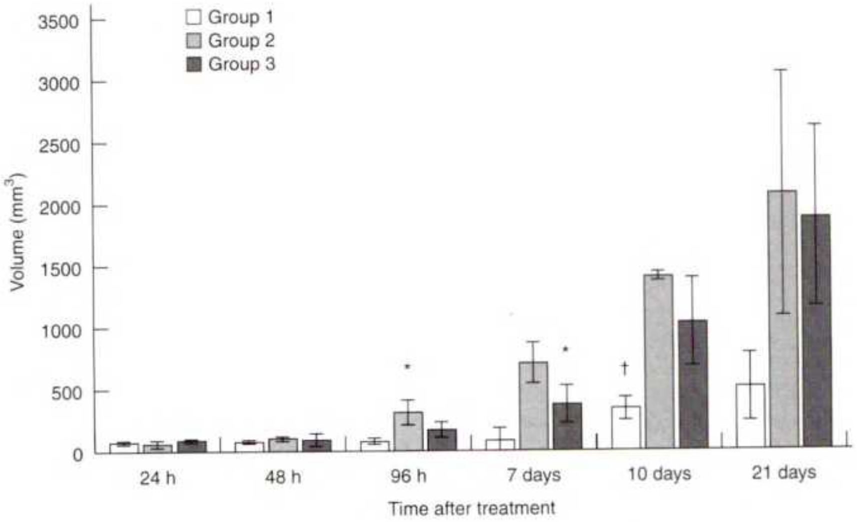

Fig. 2 Volume of untreated tumours in groups 1 (laser; $n = 30$), 2 (resection; $n = 30$) and 3 (control; $n = 30$) 24 h to 21 days after intervention. Values are median (95 per cent confidence interval). *$P < 0{\cdot}05$ *versus* group 1; †$P < 0{\cdot}05$ *versus* groups 2 and 3 (Kruskal–Wallis test)

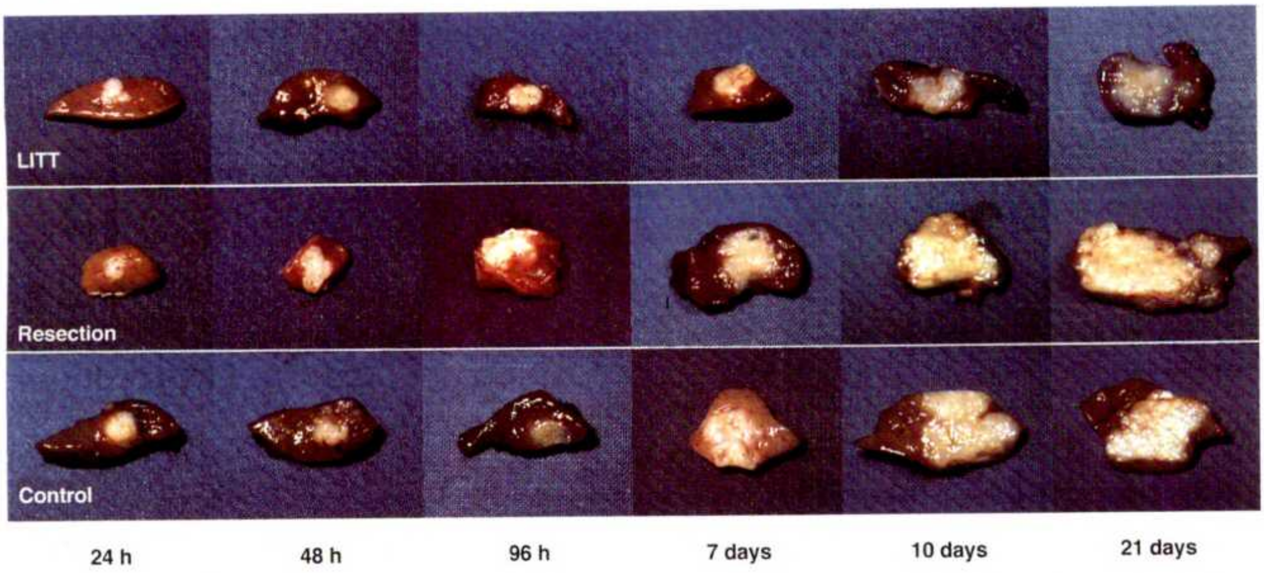

Fig. 3 Representative gross sections of untreated tumours in groups 1 (laser-induced thermotherapy (LITT)), 2 (resection) and 3 (control) 24 h to 21 days after intervention

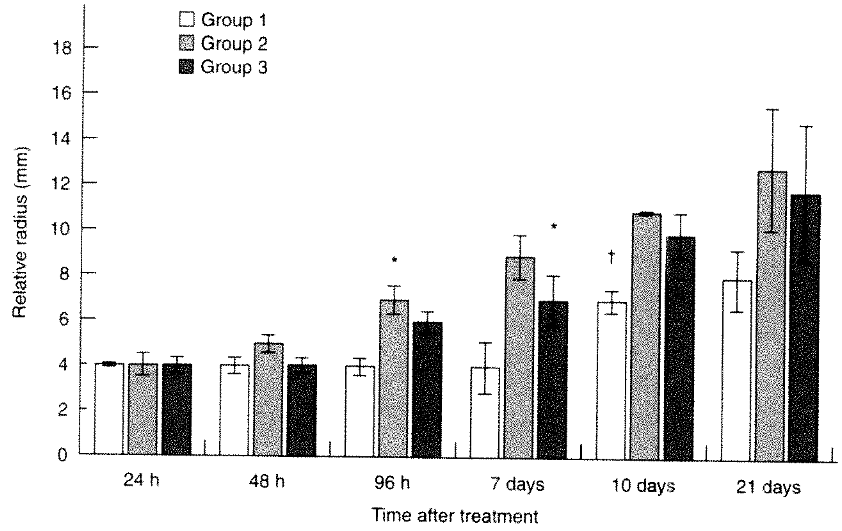

Fig. 4 Relative radius of untreated tumours in groups 1 (laser; n = 30), 2 (resection; n = 30) and 3 (control; n = 30) 24 h to 21 days after intervention. Values are median (95 per cent confidence interval). $^*P < 0{\cdot}05$ *versus* group 1; $^†P < 0{\cdot}05$ *versus* groups 2 and 3 (Kruskal–Wallis test)

with the respective pretreatment value. An increase in the relative radius of untreated tumours was calculated after 96 h in group 2 (resection) ($P < 0{\cdot}03$), after 7 days in group 3 (control) ($P < 0{\cdot}02$) and after 10 days in group 1 (laser) ($P < 0{\cdot}04$) (Dunnett test). At 96 h after the intervention, the increase in the relative radius of the untreated tumour was smaller in group 1 than in groups 2 ($P < 0{\cdot}005$) and 3 ($P < 0{\cdot}005$), the radius in group 2 animals being larger than that in group 3 ($P < 0{\cdot}023$). Compared with groups 2 (resection) and 3 (control), the reduced growth of untreated tumours in group 1 (laser) was detectable until 21 days after treatment. In contrast, growth of the untreated tumours in groups 2 and 3 was no longer different 7–21 days after the intervention (P not significant) (Scheffe test). Increases in the relative radius of untreated tumours in groups 1–3 are presented in *Fig. 5*.

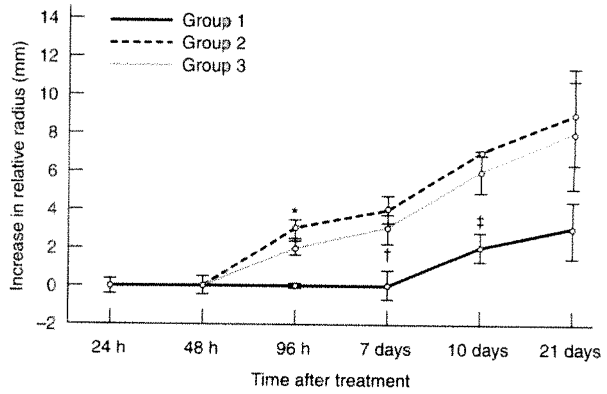

Fig. 5 Increase in relative radius of untreated tumours in groups 1 (laser; n = 30), 2 (resection; n = 30) and 3 (control; n = 30) 24 h to 21 days after intervention. Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* 24 and 48 h; $^†P < 0{\cdot}05$ *versus* 24, 48 and 96 h; $^‡P < 0{\cdot}05$ *versus* 24, 48, 96 h and 7 days (Dunnett and Scheffe tests)

Macroscopic peritoneal tumour dissemination

Histologically verified macroscopic peritoneal tumour dissemination occurred in six of 30 cases in group 1, in 20 of 30 cases in group 3 and in 24 of 30 cases in group 2.

Proliferation and apoptosis of untreated tumour

Anti-BrdU achieved immunohistochemical detection in all cases after *in vivo* incorporation of 200 mg/kg body-weight of BrdU. BrdU expression was stronger at the invasion front than at the centre of untreated tumours. BrdU expression did not differ in the three groups.

Apoptotic cell detection in the untreated tumours succeeded in all cases and was higher in areas with more tumour cell proliferation (tumour invasion front) than in those with less proliferation (tumour centre). Apoptotic cell detection did not differ between the three groups. Summarized data of the expression intensity of TUNEL and BrdU signals in the untreated tumours are given in *Table 1*.

Table 1 Proliferation and apoptosis in untreated tumours

	Signal intensity in untreated tumours*		
	Group 1 (laser)	Group 2 (resection)	Group 3 (control)
Anti-BrdU test	+ +	+ +	+ +
TUNEL test	+ +	+ +	+ +

*From 24 h to 21 days after intervention: –, no expression; +, slight expression; + +, moderate expression; + + +, strong expression. BrdU, 5-bromo-2′-deoxyuridine; TUNEL, terminal deoxyribonucleotidyl transferase-mediated deoxyuridine 5′-triphosphate (dUTP) nick end labelling

Histological examination of untreated tumours

In the conventional histological examination (haematoxylin and eosin), the tumours in group 1 (laser), group 2 (resection) and group 3 (control) showed no morphological differences. The spontaneous necrosis rate was estimated to be 20–40 per cent. The large basophilic tumour cells evidenced a clear cellular and nuclear polymorphism with a nucleus–plasma shift in favour of the cell nucleus. Numerous mitoses were found. Tumour morphology did not change with ageing or tumour size. The number and extent of spontaneous necroses increased only in the centre. There was an increased accumulation of granulocytes, macrophages and lymphocytes at the tumour invasion front compared with the tumour centre.

Discussion

Following hepatic resection of colorectal liver metastases, 30–50 per cent of patients develop an intrahepatic recurrence[5–7], probably caused by micrometastases which are detectable in up to 56 per cent of patients at operation[8]. It is also possible that surgical resection itself promotes the growth of micrometastases. Accelerated growth of liver metastases in the course of hepatic regeneration following resection of healthy liver parenchyma has been repeatedly confirmed in animal studies[10–13,23]. In the majority of related studies, tumour cells were injected directly into the animal's portal vein. Significantly accelerated growth of diffuse liver metastases was observed after hepatic resection compared with that in sham-operated controls. This effect was detected regardless of whether the intraportal tumour cell injection was performed before[11] or after[23] resection. Moreover, significantly accelerated tumour growth was found even if only 35 per cent of the healthy parenchyma was resected[23].

In the present model, tumours were deliberately created in different locations (right and left liver lobes) by subcapsular injection of tumour cells. Correspondingly, full treatment (R0 resection; complete *in situ* ablation) of the tumour in the left liver lobe (treated tumour) was performed with residual intrahepatic tumours of defined size in the right liver lobe (untreated tumour). In this model, the effect of different treatments (*in situ* ablation or resection) on the volume increase and tumour growth of untreated residual intrahepatic tumours could be recorded quantitatively. A significant increase in the size of the untreated tumours was found in the resection group after 96 h, in the control group after 7 days, and in the *in situ* ablation group after 10 days. Up to 21 days after *in situ* ablation, the tumour growth in the laser group was lower than that in the resection and control groups. Thus, *in situ* ablation led to a lower growth rate of residual intrahepatic tumour tissue than that observed following hepatic resection, with equal effectiveness in the treated tumour (R0 resection in the resection group and negative BrdU incorporation of the treated tumour in the *in situ* ablation group).

To the best of the authors' knowledge, there has been only one other experimental study in which hepatic resection was compared with LITT in the treatment of liver tumours[24]. Owing to the animal model selected, the authors could not measure the effect of the therapeutic procedure on residual intrahepatic tumour tissue. The present data show that intrahepatic growth of residual tumours after *in situ* ablation was less than that following hepatic resection or in the spontaneous course (control). Moreover, peritoneal tumour dissemination was clearly reduced after LITT compared with that after hepatic resection or in sham-operated animals. In studies using a dimethylhydrazine tumour model in rats, Möller *et al.*[24] also obtained a significantly reduced rate of peritoneal tumour dissemination after *in situ* ablation compared with hepatic resection. Macroscopic peritoneal tumour dissemination was also reduced even when *in situ* ablation was incomplete (i.e. with residual vital tumour tissue).

An altered release of systemically active growth factors may be at least partially responsible for the lower tumour growth after *in situ* ablation than after hepatic resection. During liver regeneration, quiescent hepatocytes undergo one or two rounds of replication and then become non-proliferative. Growth factors regulate this process by providing both stimulatory and inhibitory signals for cell proliferation. Epidermal growth factor, transforming growth factor (TGF) α and hepatocyte growth factor (HGF) have major effects on liver growth[25]. HGF stimulates TGF-α production in rat hepatocytes, and the mitogenic activity of HGF depends on endogenous TGF-α activity[26]. The fact that systemic factors may be responsible for tumour growth has been elucidated by *in vitro* studies. For example, tumour cells showed significantly increased cell proliferation when incubated with systemic and/or portal serum from rats previously submitted to hepatic resection[12,27]. These findings indicate that metastatic growth after hepatic resection is also influenced by circulating humoral factors. Moreover, experimental data show that extensive hepatic resection (80 per cent) is associated with an increased release of growth factors compared with minimal resection (30 per cent)[28]. In contrast to this, no differences were found between the postinterventional concentrations in the only clinical study published thus far that has compared serum HGF levels after hepatic resection and *in situ* ablation (cryotherapy) of colorectal liver metastases[29]. The fact that blood loss and subsequent fluid replacement therapy were significantly different between the two groups in this study might have influenced dilution of the serum and the concentration of growth factors. Direct detection of HGF expression in liver tissue after *in situ* ablation and hepatic resection may help to clarify this question further[30].

Moreover, it is well established that surgical trauma causes transient postoperative suppression of immune function[31]. Further studies should be performed to clarify the effect of *in situ* ablation on immunological processes in relation to intrahepatic tumour growth. Other causes of altered intrahepatic tumour growth after *in situ* ablation may be a different release of factors that directly influence the growth of metastases. For example, octreotide (a synthetic analogue of somatostatin) inhibits both hepatic regeneration and intrahepatic tumour growth after partial hepatectomy in a rat liver metastasis model[32,33]. In addition, it has been shown that the administration of angiogenesis inhibitors significantly suppresses the growth of micrometastases after hepatic resection[34]. Finally, the differential regulation of extracellular matrix synthesis during liver regeneration after hepatic resection may play an important role in terms of the different intrahepatic and extrahepatic tumour growth following *in situ* ablation and hepatic resection[35].

In conclusion, intrahepatic tumour growth and macroscopic peritoneal tumour spread were reduced and delayed after *in situ* ablation in comparison with hepatic resection and no treatment. However, further experimental *in vitro* and *in vivo* studies are required to clarify the exact causes of delayed and reduced intrahepatic and extrahepatic tumour growth following *in situ* ablation of liver metastases.

Acknowledgements

The laser equipment was kindly provided by André Roggan and Gerhard Müller, Institute of Medical Physics/Laser Medicine, University Medical Centre Benjamin Franklin, Freie Universität Berlin, Germany. This work was supported by German Research Foundation grant no. GE 932/1-2.

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Pathological appraisal of lines of resection for bile duct carcinoma

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Background: The aim of this study was to determine the most appropriate line of resection for extrahepatic bile duct carcinoma.

Methods: A retrospective review was carried out of 253 resected specimens of extrahepatic bile duct carcinoma. Carcinomas were classified histologically as invasive or non-invasive in addition to assessment of the resection margin.

Results: Tumour was present microscopically at the resection margin in 80 (31·6 per cent) of 253 cases, with 46 showing marginal involvement by non-invasive carcinoma, 20 showing invasive carcinoma at a margin, and 14 showing both. Involvement of the resection margin by invasive carcinoma was encountered only when the margin was shorter than 10 mm, whereas non-invasive carcinoma was encountered even when the margin length reached 40 mm. The observed length of microscopic extension of invasive carcinoma beyond the macroscopically evident tumour mass was limited to 10·0 mm. Median microscopic extension of non-invasive carcinoma beyond the mass was 10 mm (75th percentile 19·5 and 14·5 mm in proximal and distal directions respectively; maximum 52 mm). Margins of 20 mm could be assured to be negative proximally in 89·0 per cent of cases and distally in 93·8 per cent.

Conclusion: For eradication of invasive extrahepatic bile duct carcinoma, a 10-mm margin is required. However, additional removal of any non-invasive component requires a 20-mm margin. These guidelines should be followed in any operation performed with curative intent.

Paper accepted 11 June 2002

British Journal of Surgery 2002, **89**, 1260–1267

Introduction

A microscopically tumour-free surgical margin is usually necessary for prolonged survival in patients with bile duct carcinoma because complete eradication of the cancer is essential for cure[1–6]. To accomplish this, extensive surgical procedures are performed such as major hepatectomy including caudate lobe resection, hepatopancreatic resection or concomitant vascular resection[5,7–10]. Alternatively, limited resection has been advocated in selected patients, because this offers a fairly good prognosis provided the surgical margin is tumour-free[11–13]. Thus, outcome depends on the margin status rather than the extent of resection[3,13,14]. Aggressive procedures may enhance the likelihood of complete removal of carcinoma cells, but they may also result in more morbidity than less extensive operations. Therefore, the least extensive procedure capable of eradicating the tumour should be chosen.

Bile duct carcinoma often shows extensive microscopic spread along the bile duct beyond the macroscopic extent of the tumour mass[15,16]. This microscopic extension, which may include aggressively infiltrating and/or relatively non-invasive cancer cells, can result in tumour involvement at the resection margin even after a macroscopically successful radical resection. However, the extent of such microscopic extension has not been characterized in detail. This study investigated the correlation between resection margin status and length of the margin, and also determined the difference that might be expected between macroscopic and microscopic tumour extension in bile duct carcinoma. The goal was to determine the most appropriate resection line.

Patients and methods

Background of patients

Between January 1981 and August 2000, 253 resected specimens of extrahepatic bile duct carcinoma were submitted to the First Department of Pathology, Niigata University School of Medicine. This retrospective study was based on the pathological material in these specimens. Although available reports were taken into account, all colour photocopies and histological slides were re-evaluated for the purpose of this investigation. Carcinomas of the ampulla of Vater, gallbladder and intrahepatic bile duct were not included. Patients included 167 men and 86 women with an age range of 37–86 (mean 67·3) years. The main location of the lesion was the upper third of the duct in 68 patients, the middle third in 93, and the lower third in 92. Types of surgical procedure were pancreatoduodenectomy (*n* = 152), bile duct resection only (*n* = 51), various types of hepatectomy combined with bile duct resection (*n* = 42), and hepatopancreatoduodenectomy (*n* = 8). These operations were performed at the Niigata University Hospital and 17 local hospitals in the Niigata prefecture. According to the tumour component of the pathological tumour node metastasis (pTNM) classification, ten cases represented carcinoma *in situ* (pTis), ten were pT1, 154 were pT2 and 79 were pT3.

Pathological examination

The bile duct of the specimen was opened longitudinally, pinned to a wax board, and fixed in 10 per cent formalin immediately after resection. The macroscopic tumour mass was identified and characterized with special attention to elevation, protrusion, stenosis and irregularity in bile duct thickness. In diffusely infiltrating lesions, the extent of the tumour was defined as the region of the bile duct at which the wall thickness tapered to the level of the oedematous or fibrous mucosa without normal structures. The macroscopic distance from the superior border of the main tumour mass to the proximal cut stump of the bile duct (grossly tumour-free margin) was measured as the proximal margin. Similarly, the distance from the lower border of the main tumour to the distal cut stump was measured as the distal margin. The entire biliary tract with surrounding tissues was sectioned serially at 4-mm intervals. All sections were embedded in paraffin and stained with haematoxylin and eosin by routine methods in 220 cases, while in the remaining 33 surgical margins and representative sections were embedded and stained. The mean number of histological slides per patient was 28 (range 5–48).

Bile duct carcinoma was classified histologically as invasive or non-invasive carcinoma, with invasive carcinoma defined as involvement of the lamina propria or deeper layers. Non-invasive carcinoma was defined as atypical epithelium satisfying the following conditions (*Fig. 1*): confinement to the main tumour; an abrupt transition to the non-neoplastic epithelium; a striking degree of cytological atypia (variably sized or enlarged hyperchromatic nuclei, loss of polarity, increased nuclear : cytoplasmic ratio and prominent nucleoli) and/or structural atypia (papillary to non-papillary proliferation, complex budding and back-to-back glands). Non-invasive carcinoma in the present study is therefore equivalent to carcinoma *in situ* and severe dysplasia[15]. Regenerative or hyperplastic epithelium, histologically equivalent to low-grade dysplasia and sometimes mimicking neoplastic epithelium, was carefully excluded in serial sections, based on a gradual transition to the normal epithelium, basally aligned nuclei with pseudostratification and pronounced infiltration by inflammatory cells[15,17]. Localization of invasive and non-invasive carcinoma as demonstrated histologically was mapped separately on a full-scale photograph of the specimen (*Fig. 2*). Intramural extension was defined as invasive carcinoma spread beyond the main tumour mass; superficial extension was non-invasive carcinoma spread beyond the mass. The extent of intramural and superficial extension was measured in cases with a tumour-free resection margin. In 43 lesions involving the hepatic confluence, the longer of the extensions along the right or the left hepatic duct was considered to be the proximal extension. The resection margin of the bile duct was defined as positive when invasive or non-invasive carcinoma was identified microscopically at the cut end of the bile duct.

The correlation between length of grossly tumour-free margin and margin status was examined in all cases. Intramural and superficial extension were measured in 145 cases, excluding those with a positive resection margin or insufficient histological information.

Results are expressed as mean(s.e.). Statistical analysis was performed using Mann–Whitney *U* test and Wilcoxon signed rank test, where appropriate. $P < 0.05$ was considered statistically significant.

Results

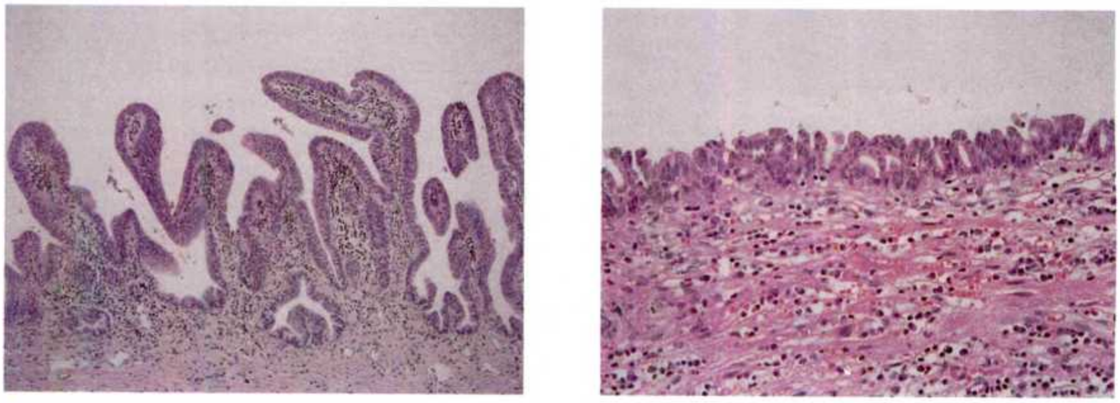
Resection margin status and grossly tumour-free margin

The proximal resection margin was evaluated in 253 cases and the distal margin in 93, excluding the 160 patients who had pancreatoduodenectomy or hepatopancreatoduodenectomy. Of the 253 cases, 80 (31·6 per cent) had a positive resection margin in either direction, including 46 with non-invasive carcinoma, 20 with invasive carcinoma and 14 with both. Of 253 cases evaluated proximally, 73 (28·9 per cent) had a positive proximal resection margin (45 with non-invasive carcinoma at this margin, 18 with invasive carcinoma and ten with both). Of the 93 cases evaluated distally, 25 (26·9 per cent) had a positive distal resection margin (15 with non-invasive carcinoma at this site, five with invasive carcinoma and five with both).

The mean(s.d.) length of the proximal margin was 8·1(8·3) mm in resection margin-positive cases and 16·0(12·0) mm in margin-negative cases ($P < 0{\cdot}001$, Mann–Whitney U test). The mean(s.d.) length of the distal margin was 6·1(5·7) mm in resection margin-positive cases and 17·8(10·2) mm in negative cases ($P < 0{\cdot}001$).

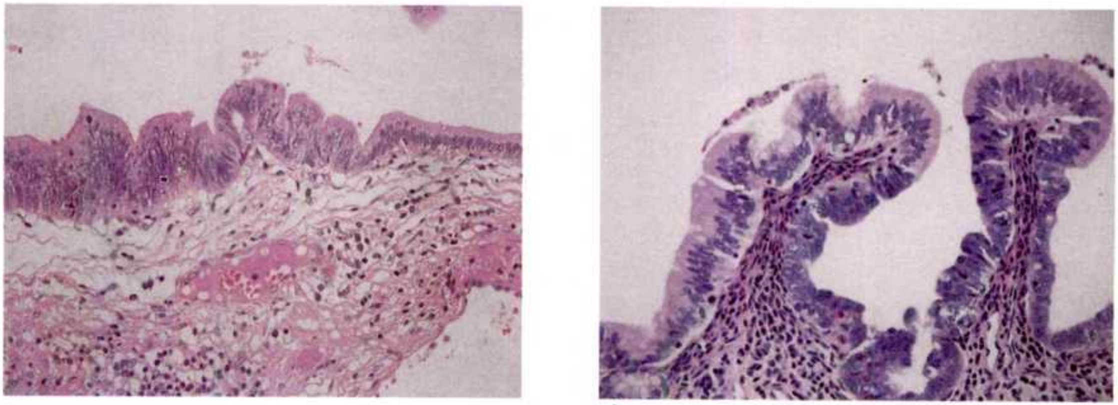
Correlation between margin length and frequency of positive resection margins

Relationships between resection margin status and the length of margin resected are shown in *Tables 1* and *2*. In 14 patients with no proximal margin, invasive or non-invasive carcinoma at the resection margin was observed in 13 and eight cases respectively; in 51 patients with a proximal margin of 1–5 mm, invasive or non-invasive carcinoma was seen eight (15·7 per cent) and 13 (25·5 per cent) cases respectively; and in 64 patients a proximal margin of 6–10 mm, there were seven (10·9 per cent) and 14 (21·9 per



a *In situ* cancer (low power)

b *In situ* cancer (high power)



c *In situ* cancer (high power)

d *In situ* cancer (high power)

Fig. 1 Microphotographs of non-invasive carcinoma (haematoxylin and eosin stain). **a** Papillary adenocarcinoma *in situ* (original magnification × 200). **b** The epithelial lining is highly atypical. The degree of cytological and structural atypia justifies a diagnosis of non-invasive carcinoma (original magnification × 400). **c** Non-invasive carcinoma forms internal overgrowth. Pseudostratification with nuclear atypia, compared with the ordinary epithelium, is conspicuous (original magnification × 400). **d** Mucosal folds are lined by non-invasive carcinoma cells. An abrupt transition to the non-neoplastic epithelium is demonstrated (original magnification × 500)

cent) cases respectively (*Table 1*). No resection margin was positive for invasive carcinoma in cases with a proximal margin exceeding 10 mm. With a proximal margin of 11–20 mm, 21–30 mm or 31–40 mm, the occurrence of non-invasive carcinoma at the resection margin was ten of 62, seven of 35, and three of 19 respectively.

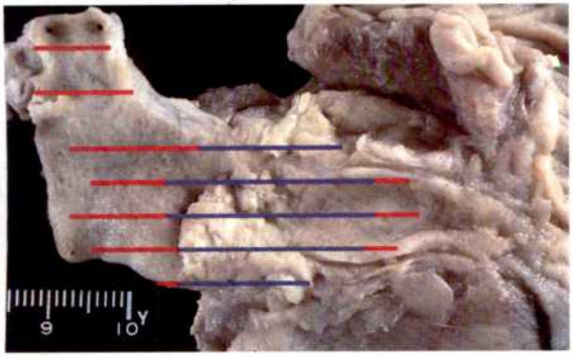


Fig. 2 Histological localization of invasive (blue line) and non-invasive (red line) carcinoma is mapped on the photograph of the resected specimen. Both carcinomas spread extensively beyond the polypoid tumour mass

Invasive carcinoma was found at the resection margin in all three patients with no distal margin, in six of 21 with a distal margins of 1–5 mm, and in one of 17 with a distal margin of 6–10 mm (*Table 2*). No invasive carcinoma was found at the cut end of a distal margin longer than 10 mm. In contrast, non-invasive carcinoma did involve the end of distal margins exceeding 10 mm in length. Non-invasive carcinoma was found at the resection margin in two of three specimens with no distal margin, in ten of 21 with a distal margin of 1–5 mm, in three of 17 with a distal margin of 6–10 mm, and in five of 31 with a distal margin of 11–20 mm.

Superficial *versus* intramural extension

Distances for intramural and superficial extension are shown in *Tables 3* and *4*; descriptive statistics are summarized in *Table 5*. Intramural extension in proximal and distal directions was present in 28 (19·3 per cent) and 25 (17·2 per cent) of 145 cases respectively. The number of cases decreased sharply in subgroups defined by extensive intramural extension. The mean length of intramural extension in proximal and distal directions was 4·6 and 4·4 mm respectively (75th percentile 5·0 mm) (*Table 5*).

Table 1 Tumour occurrence at the proximal margin, by margin length

	No. of cases ($n = 253$)	No. with a positive proximal resection margin	
		Invasive carcinoma at margin	Non-invasive carcinoma at margin
Length of proximal margin (mm)			
0	14	13	8
1–5	51	8	13
6–10	64	7	14
11–20	62	0	10
21–30	35	0	7
31–40	19	0	3
> 40	8	0	0

Table 2 Tumour occurrence at the distal margin, by margin length

	No. of cases ($n = 93$)	No. with a positive distal resection margin	
		Invasive carcinoma at margin	Non-invasive carcinoma at margin
Length of distal margin (mm)			
0	3	3	2
1–5	21	6	10
6–10	17	1	3
11–20	31	0	5
21–30	11	0	0
31–40	8	0	0
> 40	2	0	0

Table 3 Stratification of 145 tumours by length of intramural extension

	No. in proximal direction	No. in distal direction
Length of intramural extension (mm)		
0	117	120
1–5	22	21
6–10	6	4
11–20	0	0
21–30	0	0
31–40	0	0
> 40	0	0

Table 4 Stratification of 145 tumours by length of superficial extension

	No. in proximal direction	No. in distal direction
Length of superficial extension (mm)		
0	77	76
1–5	11	16
6–10	26	24
11–20	15	20
21–30	11	6
31–40	2	3
> 40	3	0

Table 5 Descriptive statistics regarding the length of intramural and superficial tumour extension

	Intramural extension		Superficial extension	
	Proximal direction	Distal direction	Proximal direction	Distal direction
Mean	4·6	4·4	14·0	13·4
Standard deviation	2·0	1·8	10·4	7·4
25th percentile	3·0	3·0	7·0	6·0
50th percentile	4·0	4·5	10·0	10·0
75th percentile	5·0	5·0	19·5	14·5
Maximum	10·0	10·0	52·0	34·0

The length of intramural extension was limited to 10 mm in both directions.

Superficial extension in proximal and distal directions was present in 68 (46·9 per cent) and 69 (47·6 per cent) of 145 cases respectively (*Table 4*). The mean length of superficial extension in proximal and distal directions was 14·0 and 13·4 mm respectively (median 10·0 mm, 75th percentile 19·5 and 14·5 mm) (*Table 5*). Superficial extension showed a highly variable range. Superficial extension in the proximal direction was not significantly different from that in the distal direction ($P = 0{\cdot}198$, Wilcoxon signed rank test); similarly, intramural extension in the proximal direction was no different from that in the distal direction ($P = 0{\cdot}427$). Three patients had superficial extension exceeding 40 mm in the proximal direction; the maximum extent was 52 mm. These patients underwent pancreatoduodenectomy for lower third lesions; two had nodular tumours and one had a diffusely infiltrating tumour. The main tumours were well, moderately and poorly differentiated adenocarcinoma. Superficial extension of the three tumours exhibited papillary proliferation in one and non-papillary extension in two. Of 145 patients with or without superficial extension, 129 (89·0 per cent) had proximal extension and 136 (93·8 per cent) had distal extension confined to within 20 mm of the mass.

Discussion

Surgeons need to achieve a tumour-free resection margin when performing curative operations for bile duct carcinoma; multivariate analysis has demonstrated that a negative surgical margin is an independent predictor of prolonged survival after operation[1,3,4,13]. Although current progress in the imaging of bile duct carcinoma offers improved preoperative delineation of the main tumour mass, accurate staging of microscopic extension along the duct remains difficult[18–21]. Instead, intraoperative histological diagnosis by means of frozen-section examination is usually used as a final confirmation of the status of the resection margin. Despite this common practice, involvement of the cut end of the resected bile duct has been noted in 14–72 per cent of cases[5,14,22,23]. The present study has focused on the correlation between the margin length and the occurrence of microscopic tumour at the cut end, as well as the observed length of microscopic extension beyond the macroscopically evident mass.

In this series a positive resection margin was observed in as many as 80 (31·6 per cent) of 253 cases. A margin was involved by invasive carcinoma in 20 cases, by non-invasive carcinoma in 46 and by both in 14. The longer the margin, the less likely it was to show tumour at the line of resection

(*Tables 1* and *2*). To procure a negative resection margin, a 10-mm proximal margin and a 10-mm distal margin sufficed for invasive carcinoma, whereas a proximal margin greater than 40 mm and a distal margin greater than 20 mm appeared to be required to avoid positivity for non-invasive carcinoma. Accordingly, biliary surgeons need to pay careful attention to the extensive spread of non-invasive carcinoma beyond the macroscopic tumour mass.

For invasive carcinoma the present study did not disclose a significant difference between macroscopic and microscopic extension in approximately 80 per cent of cases. The microscopic extent of invasive carcinoma can be predicted by macroscopic inspection, because infiltration of cancer cells usually evokes a desmoplastic reaction that results in irregular thickening of the bile duct. In the remaining 20 per cent of cases with intramural extension, however, microscopic spread was more extensive than the macroscopic tumour mass. In these cases, a mild degree of neurovascular permeation or carcinoma cell infiltration incited only minimal stromal changes, and the extent of invasion was difficult to identify macroscopically. Importantly, the length of such extension was limited to within 10 mm. Thus, a 10-mm surgical margin beyond the macroscopic tumour border is needed to eradicate invasive carcinoma cells completely.

In the present series superficial extension was observed in proximal and distal directions in 46·9 and 47·6 per cent of cases respectively. Some pathologists have observed dysplastic epithelium adjacent to infiltrating bile duct carcinoma in 50–75 per cent of cases[24–26]. In previous reports from Japan, 'mucosal' extension was present in 14–27 per cent of cases[27–29]. Differences in histological criteria for diagnosis of epithelial lesions could account for this difference in prevalence. Criteria in previous Japanese series appear to have been based on papillary structure, and in such studies the frequency of 'mucosal carcinoma' would be expected to be lower than in the present study.

Severe dysplasia and/or carcinoma *in situ* have been observed adjacent to invasive biliary carcinoma, and these lesions may be difficult to distinguish from one another both topographically and morphologically[15,26]. On the other hand, current immunohistochemical and genetic studies support a sequence of tumorigenesis proceeding from dysplasia to carcinoma *in situ*, and ultimately to invasive carcinoma[17,30,31]. In the pancreas, invasive carcinoma has been shown to be clonally derived from severe ductal dysplasia[32], and reported cases have shown progression from residual dysplasia to infiltrating carcinoma[33,34]. By analogy, in the biliary tract, severe dysplasia and carcinoma *in situ* are suspected to have the biological ability to give rise to invasive cancer. For this reason, the criteria chosen for superficial extension in the present study included carcinoma *in situ* and severe dysplasia.

The mean length of superficial extension was 13–14 (median 10) mm. Importantly, this length showed a wide distribution (maximum 52 mm). Three tumours exhibited a wide superficial extension exceeding 40 mm, and these had no distinguishing histological characteristics. Suzuki *et al.*[26] observed that the distance from the hepatic confluence to the peripheral leading edge of dysplasia and/or carcinoma *in situ* ranged from 12 to 98 mm in carcinomas at the hepatic hilum. In addition, these authors reported double biliary cancers in five of 12 patients; no multiple bile duct cancers were observed in the present series. The concept of 'field cancerization' in the biliary epithelium could play a role in the pathogenesis of tumours in the five patients reported by Suzuki *et al.*[26] and in the three patients with extremely wide superficial extension reported here, as is advocated in squamous cell carcinoma of the oesophagus and the oral cavity[35,36]. Further clonal studies are necessary to clarify the issue. In exceptional cases, even very extensive surgical margins, such as a 40-mm posterior margin and a 20-mm distal margin, may not be sufficient for complete removal of non-invasive carcinoma. This study demonstrated, however, that the 75th percentile of superficial extension was less than 20 mm, and that a 20-mm margin ensured a resection line free of non-invasive carcinoma in approximately 90 per cent of 145 cases examined. In the present series, the mean lengths of proximal and distal margins of positive resection margins were significantly shorter than those of negative resection margins. Moreover, the longer the margin, the less likely it was to find a positive resection margin. These findings may suggest that a positive resection margin is associated mainly with a short tumour-free margin rather than tumour characteristics having longer intramural and/or superficial extension.

In this study, a positive resection margin and microscopic extension due to invasive and non-invasive carcinoma were evaluated separately. Few previous reports have considered the microscopic extent of invasive and non-invasive carcinoma separately. Sakamoto *et al.*[27] demonstrated that in hilar cholangiocarcinoma mucosal extension averaged 11·5 mm whereas submucosal extension was limited to within 10 mm, similar to the present findings. However, their material was confined to hilar cholangiocarcinoma, possibly including hilar-type cholangiocellular carcinoma; additionally their examination considered only the proximal direction. The present authors therefore attempted broadly to clarify the mode of extension in both directions by extrahepatic bile duct carcinoma. Yamaguchi *et al.*[29] reported that the mean distance between the macroscopic tumour border estimated by cholangiography and the histological tumour border was 6·1 mm in the proximal direction and 6·2 mm in the distal direction. Shimada *et al.*[28] and Hayashi *et al.*[37] reported mean intramural extension lengths of 16·8 and 12·8 mm respectively. There appear to be differences in methods, including the starting point for measurement, between reports. In the present study the distance from the macroscopic tumour border to the microscopic advancing border was measured carefully using full-scale photographs. The extent of fibrosis provoked by invasive carcinoma is palpated easily during operation, and is delineated radiologically as a tumour mass[18–20]. As the present study incorporated non-fibrotic areas with invasive or non-invasive carcinoma beyond the main tumour, the findings may represent supplemental information for preoperative planning and intraoperative decision-making with regard to the resection line.

In radical resection of biliary cancer, usually only one operation is performed. Patients with residual epithelial lesions of the duct, such as severe dysplasia and carcinoma *in situ*, are rarely followed. The authors believe that not only the main tumour but also any surrounding preinvasive lesion should be removed if possible. A 20-mm margin of the bile duct would be barely obtainable in most hepatectomies performed for biliary carcinoma. Surgeons should select the optimal resection margin (10 *versus* 20 mm), based on the anatomical location of the lesion, the patient's medical condition, and whether only aggressively infiltrating cancer or the entire neoplastic lesion is to be removed. Thus, these results may guide determination of the surgical margin length in extrahepatic bile duct carcinoma.

In conclusion, histological examination of bile duct carcinoma shows extensive spread of invasive and non-invasive carcinoma beyond the macroscopic tumour mass in about 20 and 50 per cent of cases respectively. For eradication of invasive carcinoma cells, a 10-mm margin is required in both directions. For additional removal of non-invasive carcinoma cells, a 20-mm margin is recommended. These requirements should be satisfied by any operation performed with curative intent.

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Short note

Pudendal nerve terminal motor latency measurements: what they do and do not tell us

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Presented in part to the Overseas Meeting of the Section of Coloproctology of the Royal Society of Medicine, Stockholm, Sweden, May 2000

Paper accepted 11 June 2002

Introduction

Faecal continence is influenced by higher cortical centres and spinal reflexes, stool consistency, rectal compliance and capacity, and anal sphincter function. In patients with idiopathic faecal incontinence the pelvic floor and anal sphincter muscles are intact but weakened. Evidence collected over several decades has pointed to the importance of neuropathy in the aetiology of idiopathic faecal incontinence and other functional anorectal disorders. Histopathological and single-fibre electromyographic studies have demonstrated reinnervation of the external sphincter muscle[1,2] and studies of pudendal nerve terminal motor latency (PNTML) have shown slowing of motor nerve conduction in the distal part of the pudendal nerves[3].

Prolongation of PNTML is considered to be a hallmark of idiopathic faecal incontinence. PNTML is a standard part of anorectal physiology studies. However, interpreting the results of PNTML testing in the individual patient remains uncertain. Although prolongation of PNTML indicates pathology of the pudendal nerve, the nature and site of the lesion remains uncertain and it is known that the conduction velocity of a nerve may have little bearing on its functional integrity.

This study was performed to ascertain the prevalence of abnormal PNTML in a large population of patients presenting for anorectal physiology testing and to determine what measurement of PNTML does and does not tell us.

Patients and methods

Between February 1985 and October 1999, 2067 patients attended for anorectal physiology studies. Standard testing includes anorectal manometry, rectal sensation, electromyography, determination of PNTML and transanal ultrasonography. Transanal ultrasonography has been performed since March 1995. More than 99 per cent of investigations have been performed by one physiologist (G.H.). In this unit a nerve latency of more than 2·2 ms has been found to indicate neuropathy[4].

Statistical analysis was carried out using the Statistical Package for the Social Sciences for Windows version 9 (SPSS, Chicago, Illinois, USA). The relationships between different variables were investigated using linear regression analysis and Pearson's correlation coefficient. Parametric unpaired *t* tests were used to compare means (as groups were well matched and normally distributed).

Results

In 365 cases (18 per cent) determination of PNTML was not carried out, provoked too much pain or failed to yield a measurable response on either the left or right. Some 1055 patients (51 per cent) had normal latency bilaterally, 414 (20 per cent) had unilateral neuropathy and 233 (11 per cent) bilateral neuropathy. Thus, at least 31 per cent of the 2067 patients had a prolonged PNTML. In the 1702 patients who had latency measurements on both the left and right side, the PNTML rose slightly with age in all three groups. This rise in age was significant only in the group with normal latency ($P < 0{\cdot}001$) (*Fig. 1*). The mean age of patients with bilateral neuropathy was 5 years more than that of patients with unilateral neuropathy and 10 years greater than that of those with normal latency ($P < 0{\cdot}001$). This may indicate that the unilateral group represents a stage in a transition to bilateral neuropathy.

In cases of bilateral neuropathy there was a significant reduction in mean voluntary squeeze pressure, amounting to 10 cmH_2O, compared with normal latency ($P < 0{\cdot}001$) (*Table 1*). However, 31 per cent of patients with bilateral neuropathy had mean squeeze pressures in the normal range (greater than 50 cmH_2O) and 49 per cent of those with normal PNTML and an intact sphincter had squeeze pressures below the normal range. Patients with unilateral and bilateral neuropathy had a significant reduction in mean resting pressure in the anal canal. The magnitude of the reduction was small, amounting to only 4–5 cmH_2O, compared with patients with normal latency ($P < 0{\cdot}001$) (*Table 1*).

Conclusion

The prevalence of prolonged PNTML in a large group of patients presenting for anorectal physiology studies is at least 20 per cent with unilateral neuropathy and 11 per cent with bilateral neuropathy. The PNTML increased slightly with age in the three groups (significant only in the group

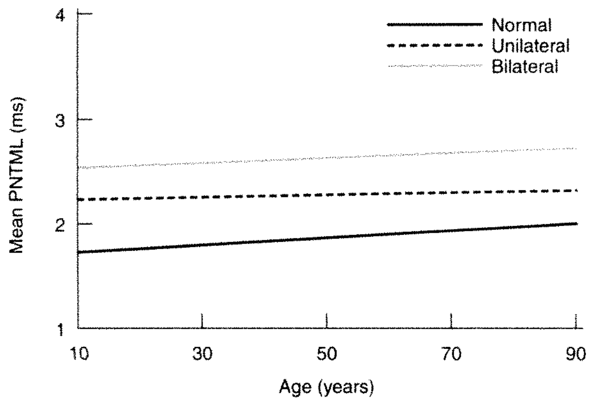

Fig. 1 Linear regression showing the effect of age on mean pudendal nerve terminal motor latency (PNTML) in patients with normal latency ($P < 0{\cdot}001$), unilateral neuropathy ($P = 0{\cdot}204$) and bilateral neuropathy ($P = 0{\cdot}249$) (Pearson's correlation)

Table 1 Mean anal canal pressure in patients with normal latency, unilateral or bilateral neuropathy

	Mean resting pressure (cmH$_2$O)	Mean squeeze pressure (cmH$_2$O)
Normal latency	63·3(27·1)	51·7(33·9)
Unilateral neuropathy	58·1(29·2)*	46·6(31·3)
Bilateral neuropathy	59·4(28·4)*	41·7(28·6)*

Values are mean(s.d.). *$P < 0{\cdot}001$ *versus* normal latency (unpaired t test)

with no neuropathy). The fact that patients with bilateral prolonged PNTML had reduced squeeze pressure generated in the external anal sphincter muscle compared with controls supports the concept that a pathological process affecting conduction in the pudendal nerve impairs sphincter function. The internal anal sphincter is considered to contribute 80 per cent of the resting tone in the anal canal. It has an autonomic innervation and is thus unaffected by pudendal neuropathy. The small drop in resting pressure seen in patients with neuropathy is in keeping with the contribution of the external sphincter to resting tone.

The finding that 31 per cent of patients with bilateral prolonged PNTML have squeeze pressures in the normal range and that 49 per cent of those with a normal PNTML have squeeze pressures below the normal range means either that this test for neuropathy is insensitive or that neuropathy is relatively unimportant. Thus, for an individual patient, the PNTML is frequently not helpful in the understanding of their faecal incontinence, and the authors suggest that newer – more specific and sensitive – tests of the sphincter muscle innervation are required.

Some 20 years after the development of PNTML testing, it can be concluded that the concept of a neuropathic process affecting pelvic floor function remains correct. This neuropathy appears to progress with time. More sensitive tests of nerve and muscle function are required to gain further understanding of the pathological process; a change in practice and tools is required. Knowledge of the PNTML contributes little to the management of pelvic floor functional disorders in individual patients, although it may be of prognostic value when surgical treatment of idiopathic faecal incontinence is being considered[5].

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Outcome of segmental colonic resection for slow-transit constipation

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Background: The standard surgical treatment for slow-transit constipation (STC) is subtotal colectomy and ileorectal anastomosis. A segmental resection may serve the same purpose, but with a reduced risk of side-effects such as diarrhoea or incontinence. The aim of this study was to evaluate the functional results following segmental resection in a consecutive series of patients with STC.

Methods: Selection criteria included prolonged segmental transit on oral ^{111}In-labelled diethylene-triamine penta-acetic acid scintigraphic transit study, and disabling symptoms resistant to medical therapy and treatment of outlet obstruction. Twenty-eight patients (26 women, median age 52 years) were treated with segmental resection and followed prospectively with a validated questionnaire.

Results: After a median of 50 (range 16–78) months, 23 patients were pleased with the outcome. The median (range) stool frequency increased from 1 (0–7) to 7 (0–63) per week ($P < 0.001$). The number of patients passing hard stools and straining excessively decreased ($P = 0.016$ and $P = 0.041$, respectively). The median incontinence score was unchanged. Rectal sensory thresholds were higher in patients in whom the treatment failed ($P < 0.001$).

Conclusion: With a symptomatic relief comparable to that after ileorectal anastomosis and less severe side-effects, segmental colectomy may be a better alternative for selected patients with STC. Thorough preoperative evaluation is important and impaired rectal sensation may predict a poor outcome.

Presented in part to the annual meeting of the Swedish Surgical Society, Strömstad, Sweden, August 1998
Paper accepted 11 June 2002 British Journal of Surgery 2002, **89**, 1270–1274

Introduction

Subtotal colectomy with ileorectal anastomosis (IRA) is the standard surgical treatment for selected patients with slow-transit constipation (STC). The operation is successful in 50–90 per cent after at least 3 years' follow-up[1–4]. A number of patients, however, experience postoperative side-effects such as diarrhoea, faecal incontinence and frequent stools. Postoperative diarrhoea has been reported in up to 30 per cent and faecal incontinence in approximately 15 per cent[1,3,5,6]. A stool frequency of five per day is not unusual. Symptoms such as bloating and abdominal pain may persist after surgery[1–5]. In addition, recurrent constipation has been reported in up to 30 per cent after 3 years of follow-up[2]. Ordinary complications after abdominal surgery may also occur; intestinal obstruction is seen in about 20 per cent of patients after IRA[3,5].

In theory, a limited colonic resection would reduce side-effects such as diarrhoea and incontinence. A more normal stool consistency and frequency would be achieved by maintaining some colonic resorptive capacity and storage function. Furthermore, a limited colonic resection reduces the deperitonealized area and may reduce the risk of postoperative adhesions.

Scintigraphic transit studies have identified different patterns of segmental slow transit, such as a delay in the right colon[7,8], in the transverse colon and splenic flexure[9], or more distal delay in the left or rectosigmoid colon[7–10]. The finding of relatively normal transit in a segment of the colon might be an argument for performing a limited resection.

Few prospective studies have addressed the symptomatic outcome of segmental resection for STC[11,12]. The aim of this prospective study was to evaluate functional outcome and patient satisfaction after segmental colonic resection.

Patients and methods

Patients

Twenty-eight patients (26 women and two men; median age 52 (range 32–79) years) with intractable constipation underwent segmental colectomy between 1993 and 1999. The median duration of symptoms was 17 (range 1–50) years. The median age at onset of constipation was 35 (range 8–59) years. Symptoms included infrequent defaecation, hard stools, excessive straining, abdominal pain and bloating. All patients had tried dietary measures and laxatives with inadequate effect.

The history included surgery for haemorrhoids in five patients, anal fissure in two, hysterectomy in five, high anterior resection in two and rectopexy in four patients.

Preoperative evaluation

After organic colon disease had been excluded by barium enema or colonoscopy, the patients were assessed according to a standardized protocol including anorectal manovolumetry[13], electromyography of the pelvic floor[14], video defaecography[15], radio-opaque marker transit study[16] and oral scintigraphic segmental transit study. A strain/squeeze index (100 × strain amplitude/squeeze amplitude) was calculated from the electromyographic measurements for the external anal sphincter and the puborectalis muscle, in the left lateral and sitting positions and while expelling a balloon. A mean value exceeding 50 was considered to represent paradoxical activity[14]. The rectal evacuation rate on video defaecography was evaluated by computer-based area calculation. The area of the lower 8 cm of the rectum with homogenous contrast was calculated (in pixels) at rest, after the initial evacuation (i.e. first strain) and after the total evacuation period. The evacuation rate was expressed as percentage area evacuated per second[15]. The gastrointestinal transit time, as measured by radio-opaque markers[16], exceeded the normal range in all but two patients. These two patients had a transit time close to the upper limit of the normal range and a clinical picture of STC. The scintigraphic study was done to assess segmental colonic transit. A suspension of 15 MBq ^{111}In-labelled diethylenetriamine penta-acetic acid (DTPA) was ingested and scans were obtained after 1, 2, 3, 6 and 24 h, and then once every 24 h until the radioactive marker had been evacuated. The patients in this series were found to have a marked delay in either the left or the right colon and a less impaired transit in the remaining segments.

A coexisting outlet obstruction was treated primarily with biofeedback[17] in ten patients, with transanal repair of a rectocele[18] in four, and with anorectal myectomy in one patient. The symptomatic relief of these procedures was unsatisfactory, indicating that slow transit was a major or contributing cause of the symptoms.

The study was approved by the ethics committee of the University of Uppsala.

Surgical procedures and follow-up

Twenty-six left and two right hemicolectomies were performed. In six patients a suture rectopexy was performed together with the left hemicolectomy. The indications for rectopexy were rectal prolapse in one and intra-anal intussusception on defaecography, together with symptoms in five patients (incomplete rectal emptying in five, faecal incontinence in two, rectal pain in three). The anastomosis was made between the mid-transverse colon and the upper rectum at the level of the sacral promontory or, in right hemicolectomy, between the distal ileum and the mid-transverse colon.

The patients were followed prospectively with a validated questionnaire[19] before and after surgery. In addition, they rated their satisfaction with the operation and stated whether they would recommend the operation to a relative with similar symptoms.

Early failure occurred in three patients, who underwent further surgery before follow-up. The remaining 25 patients were followed up after median 50 (range 16–78) months. An index of constipation-related symptoms derived from the questionnaire, using 11 questions with good reproducibility, was also used to assess functional outcome[17]. The index included enema use, excessive straining, digitation, abdominal or rectal pain, pain at or after defaecation, rectal bleeding, flatus, and impact on well-being or social life (one point for each symptom).

Statistical analysis

Non-parametric methods were used. Treatment effects were evaluated using NcNemar's test for categorical variables and Wilcoxon's matched pairs test for numerical values. The Mann–Whitney *U* test was used to compare groups. $P < 0.05$ was considered significant. Data are presented as median (range). STATISTICA™ software was used for the calculations (StatSoft, Tulsa, Oklahoma, USA).

Results

Clinical outcome

There were no deaths in hospital or within 30 days, and no major complications that necessitated reoperation. The median postoperative hospital stay was 7 (range 4–30) days.

The operation was considered a failure in five patients because each finally required further surgery. Three of these patients underwent surgery before follow-up; one had a colostomy, one an appendicostomy and one patient underwent several operations without resolving the constipation. The latter patient was later diagnosed with gastrointestinal pseudo-obstruction on histological examination. Two patients had recurrent constipation, with gradual onset of symptoms after 6 and 12 months. One of these patients, who reported a fair result at follow-up, later had an IRA; the other is due to have an IRA.

Six patients were subsequently readmitted to hospital, of whom two had surgery for small bowel obstruction and one underwent repair of an incisional hernia.

Functional outcome

The outcome was considered as excellent by ten patients, good by seven and fair by another seven patients. Four patients reported a poor result. Twenty-three patients would recommend the operation to a relative.

The median (range) stool frequency increased from 1 (0–7) to 7 (0–63) per week ($P < 0{\cdot}001$). Twenty of 25 patients had a postoperative stool frequency between three per day and three per week. A reduction was seen in the number of patients with excessive straining ($P = 0{\cdot}041$) as well as the percentage of time spent straining at defaecation ($P = 0{\cdot}025$). The incidence of bloating and painful defaecation was reduced ($P = 0{\cdot}021$ and $P = 0{\cdot}013$, respectively) whereas the proportion of patients with abdominal pain was unchanged (*Table 1*). The number of patients with hard stools decreased from 12 to three ($P = 0{\cdot}016$) and the number with normal stool consistency increased from one to seven ($P = 0{\cdot}041$). Furthermore, the use of laxatives and enemas decreased (*Table 2*). The median (range) symptom index at follow-up was 4·5 (0–10) compared with 6·5 (3–11) before surgery ($P < 0{\cdot}001$).

Faecal continence improved in eight patients and deteriorated in five. The Miller incontinence score increased from a median of 1·0 to 3·0 ($P = 0{\cdot}46$). One patient, who underwent left hemicolectomy, developed diarrhoea after operation with about nine loose stools daily.

The median (range) preoperative stool frequency was 0 (0–0·5) per week in those whose operation subsequently failed and 1 (0–7) in patients who had a successful outcome ($P < 0{\cdot}001$). The median (range) percentage of time straining at defaecation was 100 (95–100) and 82 (10–100) per cent respectively ($P < 0{\cdot}05$). There were no other differences in preoperative symptoms between those who had a successful outcome and those who did not. Furthermore, there were no differences with respect to the patient's age at onset of constipation (before or after 30 years of age), previous surgery or primary treatment with either biofeedback or previous repair of a rectocele.

Table 1 Functional outcome of segmental colonic resection in 25 patients with slow-transit constipation

	Before operation	Follow-up	*P*
Stool frequency (per week)*	1·0 (0–7)	7·0 (0–63)	< 0·001†
Abdominal pain	19	14	0·074‡
Bloating	24	18	0·021‡
Excessive straining	19	13	0·041‡
Percentage time straining*	88·5 (10–100)	52·5 (0–100)	0·025†
Painful defaecation	13	5	0·013‡

*Values are median (range). †Wilcoxon's matched pairs test; ‡McNemar's test

Table 2 Use of medication for constipation in 25 patients before and after segmental resection for slow-transit constipation

	Before operation	Follow-up	*P**
No laxatives/enemas	0	14	< 0·001
Bulking agents	16	5	0·006
Motor stimulants	14	3	0·010
Enemas, all types	15	3	0·002
Combination of laxatives	15	1	< 0·001

*McNemar's test

All five patients whose operation failed had impaired rectal sensory function on preoperative manovolumetry, whereas four of the 23 patients with a successful outcome had impaired rectal sensation ($P < 0{\cdot}001$) (*Table 3*). There was no difference in anal canal pressures or the threshold pressure required to elicit the rectoanal inhibitory reflex. The initial rate of rectal evacuation on defaecography was lower in patients whose operation failed than in the other patients ($P < 0{\cdot}05$) (*Table 3*). The median strain/squeeze index on electromyography was within the normal range in both groups (*Table 3*). The gastrointestinal transit time did not differ between the groups (*Table 3*).

Of the two patients who had a right colonic transit delay identified on scintigraphy, treated with right hemicolectomy, one had a fair result and the other was among the early failures. One of the two patients with a marginally prolonged transit time had an excellent outcome and the

Table 3 Results of preoperative evaluation in relation to outcome of surgery

	Failure (*n* = 5)	Success (*n* = 23)	*P***
Manovolumetry			
Threshold pressure for rectal filling sensation (cmH$_2$O)*	50 (30–60)	20 (5–35)	< 0·001
Threshold pressure for urge to defaecate (cmH$_2$O)†	> 60	35 (20–60)	< 0·001
Defaecography‡			
Initial rectal evacuation rate (% area evacuated per s)	1·9 (0–3·4)	5·2 (0–11·4)	0·025
Total rectal evacuation rate (% area evacuated per s)	1·6 (0–2·5)	2·6 (0·5–8·3)	0·153
Electromyography			
Strain/squeeze index§	3·0 (0–52)	21·5 (0–118)	0·113
Radio-opaque marker study			
Transit time (days)¶	5·4 (5·0–6·3)	5·9 (4·2–6·5)	0·380

Values are median (range). *Normal range 10–25 cmH$_2$O (maximum measurement 60 cmH$_2$O). †Normal range 20–50 cmH$_2$O (maximum measurement 60 cmH$_2$O). ‡Calculated for five failures and 16 successes. §Normal value ≤ 50. ¶Normal value ≤ 4·7 days for women and ≤ 2·8 days for men. **Mann–Whitney *U* test

other a fair result, and both recommended the operation. Of the six patients who had a rectopexy with left hemicolectomy, three had a good or excellent result and three had a fair result; all six recommended the operation.

Discussion

Of 28 patients in the present study who underwent segmental colectomy for constipation, 23 were satisfied with the results. The stool frequency increased to median of one per day among the 25 patients followed for a median of 50 months, and was achieved either without laxatives or with only bulking agents in 19 of these patients. Only one patient had persisting postoperative diarrhoea. The median incontinence score did not change significantly. Abdominal pain and bloating remained common symptoms after surgery, as is also the case after IRA.

The present results are comparable to those of other studies that have evaluated IRA[1–6]. Some of the side-effects described after IRA appeared to be less frequent, in accordance with other reports on segmental resection for STC[12,20]. In a study by de Graaf *et al.*[11], 18 patients with delayed transit in the left colon underwent partial left-sided colectomy and 24 patients, with a uniform delay, had subtotal colectomy. Postoperative diarrhoea or incontinence occurred in two patients in the left-sided colectomy group compared with five in the subtotal colectomy group. Recurrent constipation occurred in three and seven patients respectively. Similarly, abdominal pain and bloating were about half as frequent in the left-sided colectomy group. Data concerning postoperative stool frequency were not presented in that study.

A limited colonic resection for segmental STC seems to be a reasonable therapeutic option. In patients with combined STC and outlet obstruction, the authors' policy is first to treat the outlet obstruction with biofeedback or rectocele repair. Some patients respond well to such treatment and may not need a colonic resection. Although Lubowski *et al.*[3] and others have found it unnecessary to treat outlet obstruction with biofeedback before IRA, it is not clear whether this is also the case before segmental resection.

The importance of a thorough evaluation of these patients cannot be emphasized enough. The radio-opaque marker method described is suitable for the assessment of overall colonic transit time. However, scintigraphic transit studies have advantages when it comes to assessing segmental transit. Many patients with constipation have a long colon. Identifying the correct position of markers in different colonic segments may be difficult on a single abdominal radiograph. The colon can be outlined more easily on a scintigraphic image and frequent scans can be obtained without adding to the radiation dose. Since the single dose of radioactive marker is taken under the supervision of laboratory staff, the method is also less subject to poor patient compliance. In addition, the scintigraphic study confirms the prolonged total colonic transit time diagnosed by the radio-opaque marker study. Upper gastrointestinal function was not assessed in the present study. Redmond *et al.*[5], however, reported poorer results of IRA in a group of patients with generalized intestinal dysmotility, as evaluated by oesophageal and small intestinal manometry and electrogastrography, compared with those with an isolated colonic inertia.

Both clinical data and preoperative investigation indicated that patients with a poor outcome had a more profound disturbance in colorectal function. In the failure group there were only five patients, which makes statistical comparison difficult. Impaired rectal sensory function has been found to correlate with a poor outcome after IRA[21,22] and the current results also suggest that rectal sensory function may predict outcome.

The present study shows that segmental colonic resection is a surgical option for some patients with intractable STC, and may be superior to IRA. A thorough evaluation, including ^{111}In-labelled DTPA scintigraphy to assess segmental colonic transit, provides a diagnostic basis for selection of patients suitable for segmental resection. Further controlled, prospective studies with long-term follow-up are needed to verify the results and to compare segmental resection with IRA.

Acknowledgements

This study was supported by the Swedish Research Council, project no. K 2000-27x-13082-02B.

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Scintigraphic assessment of antegrade colonic irrigation through an appendicostomy or a neoappendicostomy

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Background: The aim of this study was to evaluate large bowel transport following antegrade colonic irrigation with a new scintigraphic technique.

Methods: Ten patients (eight with severe constipation, two with faecal incontinence; median age 47 (range 41–66) years) treated with antegrade colonic irrigation took ^{111}In-labelled polystyrene pellets to label the bowel contents. ^{99m}Tc-labelled diethylenetriamine penta-acetate was mixed with the irrigation fluid to map its distribution within the large bowel. Scintigraphy was performed before and after a standardized irrigation procedure. The large bowel was divided into four segments. Assuming ordered evacuation of the large bowel, the contribution of each colonic segment to total evacuation was expressed as a percentage of original segmental count. The segmental contributions were added to reach a total defaecation score (range 0–400).

Results: The median defaecation score was 350, corresponding to complete emptying of the rectosigmoid, descending colon, transverse colon, and half of the caecum and ascending colon. The retained irrigation fluid was located throughout the large bowel. Back-flow to the ileum was observed in four patients.

Conclusion: This study used a new scintigraphic technique to assess large bowel transport following antegrade colonic irrigation. Antegrade colonic irrigation induces highly effective emptying even in patients with severe constipation.

Paper accepted 13 June 2002

British Journal of Surgery 2002, **89**, 1275–1280

Introduction

Antegrade colonic irrigation through an appendicostomy was introduced by Malone *et al.*[1] in 1990. Since then, the Malone antegrade continent enema (MACE) has proved to be safe and effective in children suffering from faecal incontinence or chronic constipation due to spina bifida or anorectal malformation[2–8]. More recently, it has been used in the treatment of neurogenic colorectal dysfunction[9–11] and chronic idiopathic constipation in adults[12,13].

Colorectal scintigraphy provides precise quantitative information about the pattern and effectiveness of large bowel transport that is difficult to obtain by other means[14–16]. The aim of the present study was to evaluate large bowel emptying following antegrade colonic irrigation by using a new scintigraphic technique. A second aim was to map the distribution of retained irrigation fluid by means of a dual-isotope technique.

Patients and methods

Patients

From January 1993 to December 2000, 32 patients underwent the Malone operation (25 women and seven men; median age at the time of operation was 42 (range 16–66) years). At 31 December 2000, 19 patients still used antegrade colonic irrigation (median time from operation 23 (range 1–96) months). These 19 patients were invited to participate in the study. Ten patients agreed (nine women and one man; median age 47 (range 41–66) years; median time from operation 14 (range 3–72) months). The stoma had been made from the appendix in six patients, from the divided terminal ileum in three[17], and one patient had a caecal flap[18]. Before operation patients were evaluated by means of anorectal physiology, endoanal ultrasonography, defaecography and radiologically determined colorectal transit time[19,20]. Eight patients suffered from severe constipation with prolonged colonic transit time and two were incontinent to solid stools daily or several times per week.

Patients were interviewed using a colorectal function questionnaire both before operation and once irrigation had been established. General satisfaction with the MACE was noted.

The protocol was approved by the Aarhus County ethics committee and was in accordance with the Declaration of Helsinki.

Radiological colonic transit time

The total gastrointestinal transit time and the segmental colorectal transit times were determined as described by Abrahamsson *et al.*[20]. Patients maintained their normal irrigation regimen while taking ten radio-opaque markers each day for six consecutive days. They were instructed to avoid colonic irrigation from 48 h before plain abdominal radiography was performed on day 7.

Scintigraphic procedure

Patients swallowed ^{111}In-labelled polystyrene particles in 100 ml water on two different days. The first dose of 2·6 MBq given 48 h before investigation to patients with normal colonic transit time, and 3·3 MBq was given 72 h before investigation to patients with prolonged colonic transit time. All patients took a second dose of 2·6 MBq 24 h before the investigation. They were instructed to avoid colonic irrigation from 48 h before the investigation.

The irrigation procedure used in the study was standardized. Some 1100 ml tap water (37°C) was mixed with 10 MBq ^{99m}Tc-labelled diethylenetriamine penta-acetate. The irrigation bag was hung 100 cm above the stoma on a strain gauge connected to a computer that recorded infused volume and flow rate of the irrigation fluid. The gross weight of faecal output was determined.

Scintigraphy was performed before and after colonic irrigation with the patient in supine position using a two-headed γ camera (Picker Prism™ 2000XP; Phillips Medical System, Cleveland, Ohio, USA) equipped with a parallel-hole medium-energy collimator. Anterior and posterior images were obtain using a 15 per cent energy window over the 140-keV ^{99m}Tc photo peak and the sum of two 20 per cent energy windows over the 174- and 247-keV ^{111}In photo peaks. The acquisition time was 10 min (five frames of 2-min duration). If steady state during the acquisition period could be assumed, the frames were added to give a static image. Anterior images before and after irrigation are shown in *Figs 1* and *2a,b*.

Data analysis

Each image of the large bowel was divided into four regions of interest for integration of radioactivity in accordance with the convention used in radiographic segmental colonic transit[20] and previous scintigraphic studies[21,22]: (1) the caecum and ascending colon including the right colic flexure, (2) the transverse colon, (3) the descending colon including the left colic flexure, and (4) the rectosigmoid. Regions of interest were delineated manually.

To correct for tissue attenuation, the geometric mean was calculated for each segment as the square root of the product of counts registered in the anterior and posterior region of interest of the colonic segment[23]. Background subtraction was not performed. In a pilot study a scatter fraction of 0·34 was estimated experimentally to correct for scatter radiation of ^{111}In at the ^{99m}Tc window. No correction was used for radiation of ^{99m}Tc registered at the ^{111}In window.

Defaecation score

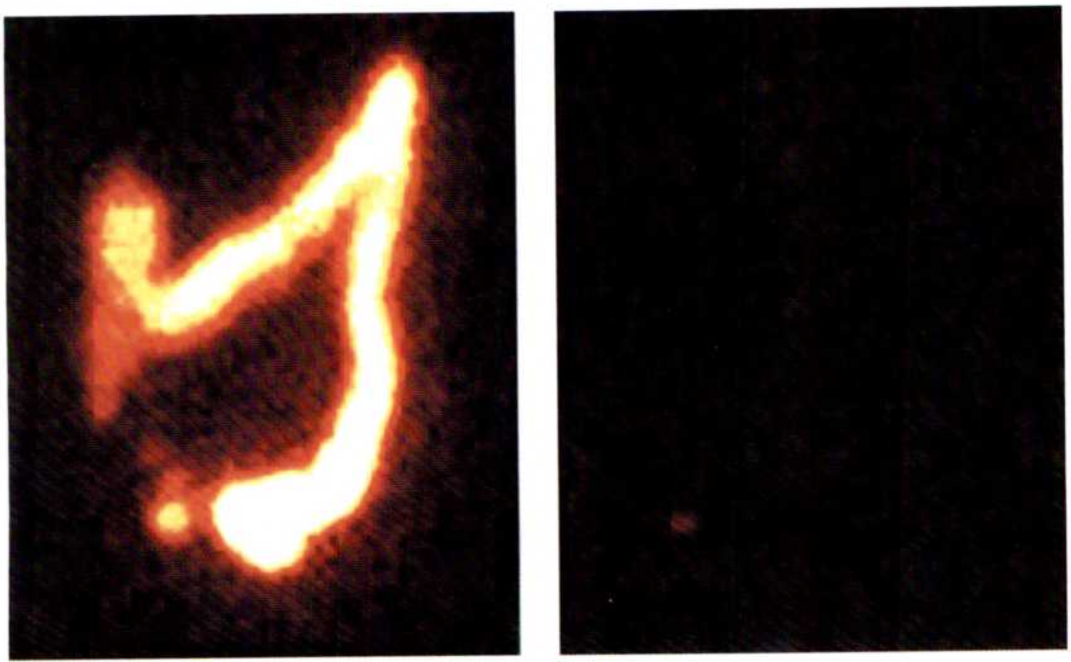
A defaecation score was calculated to quantify large bowel emptying in a single value. The total number of counts evacuated was measured. Assuming ordered evacuation of the large bowel, the contribution of each colonic segment to the overall evacuation was expressed as a percentage of the segmental counts before irrigation. The contributions of each segment were added to reach a total defaecation score (range 0–400). Thus, a defaecation score of 400 indicated complete evacuation of radioactivity in the large bowel, while a defaecation score of 150 indicated complete evacuation of radioactivity in the rectosigmoid and 50 per cent evacuation of radioactivity in the descending colon.

Distribution of retained irrigation fluid

The dual-isotope technique allowed transformation of the regions of interest from the ^{111}In images to the corresponding scatter-corrected ^{99m}Tc images. Thus, the segmental distribution of the retained irrigation fluid was determined and expressed as a percentage of the scatter-corrected total ^{99m}Tc counts. The images were examined for possible reflux of irrigation fluid into the ileum.

Radiation dose

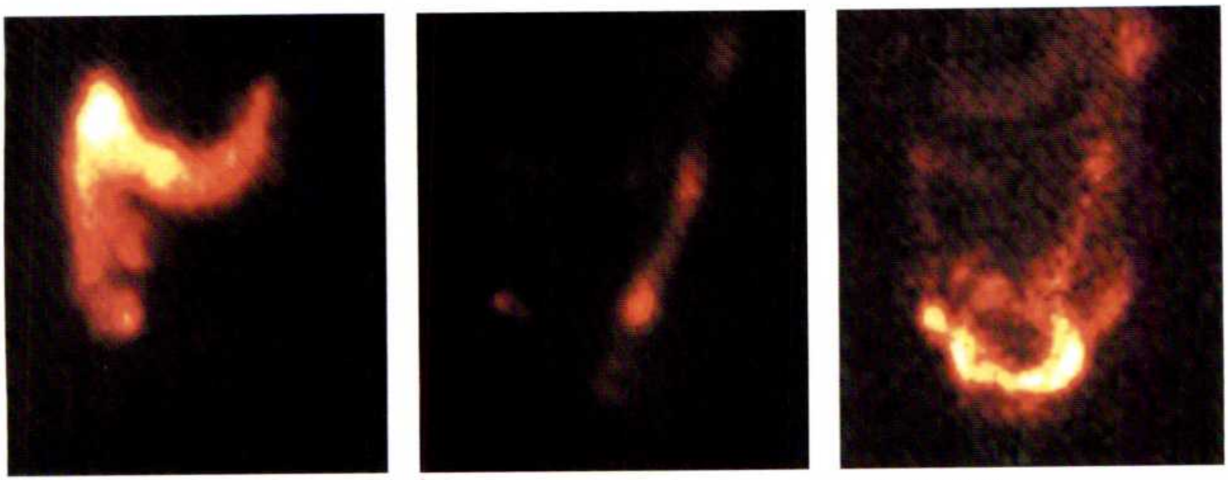
Patients received an effective whole-body dose from the radiopharmaceuticals and the X-rays of 2–6 mSv.



a Before irrigation

b After irrigation

Fig. 1 Anterior views of patient with idiopathic faecal incontinence. ^{111}In-labelled bowel contents **a** before irrigation and **b** after irrigation



a Before irrigation

b After irrigation

c Retained fluid

Fig. 2 Anterior views of patient with chronic idiopathic constipation (ileal conduit). **a** ^{111}In-labelled bowel contents before irrigation; radiolabelled polystyrene pellets have reached the left colic flexure. **b** ^{111}In-labelled bowel contents after irrigation; only a few faeces remain in the descending colon. **c** ^{99m}Tc images of the retained irrigation fluid in the same patient after irrigation; reflux of irrigation fluid through the ileocolonic anastomosis to the ileum is present, producing overlap of segments

Results

Scintigraphic determination of large bowel emptying

The median volume of tap water used in the study was 1092 (range 1071–1109) ml, median flow rate was 3·7 (range 2·7–5·5) ml/s and median gross weight of the faecal output was 1050 (range 426–1361) g.

The ^{111}In images before irrigation formed a variable image of the large bowel. In five of ten patients the rectosigmoid area was not clearly visible. In these patients the rectosigmoid regions of interest were approximated in

Table 1 Segmental distribution of counts before the washout

	Segmental distribution (%)
Caecum and ascending colon	34 (15–70)
Transverse colon	23 (6–45)
Descending colon	34 (3–51)
Rectosigmoid	6 (1–31)

Values are median (range)

Table 2 Retained irrigation fluid in six patients without reflux to ileum

	Segmental distribution of retained fluid (%)
Caecum and ascending colon	18 (12–47)
Transverse colon	12 (8–17)
Descending colon	31 (14–66)
Rectosigmoid	27 (8–60)

Values are median (range)

size and position, and if necessary adjusted after inspecting the ^{99m}Tc images of the retained fluid after irrigation. The segmental distribution of counts is shown in *Table 1*. No ^{111}In counts could be related to the small bowel before and after irrigation.

The median defaecation score was 350 (range 29–369). This indicates complete evacuation of the radioactivity from the rectosigmoid, the descending colon and the transverse colon, and 50 per cent evacuation of radioactivity from the caecum and ascending colon.

Reflux of ^{99m}Tc-labelled irrigation fluid was seen in all four patients who had a neoappendicostomy (three ileal conduit, one caecal flap). Back-flow to the ileum caused overlap of segments, making determination of the segmental distribution of the retained irrigation fluid impossible in those patients (*Fig. 2c*). The segmental distribution of the retained irrigation fluid in six patients without reflux is given in *Table 2*. A considerable, but undetermined, proportion of the irrigation fluid was evacuated with the faeces.

Radiological colonic transit time

Before operation, eight of the ten patients had prolonged colonic transit time. With antegrade irrigation treatment, the median total gastrointestinal time during the normal irrigation regimen was 3·1 (range from 1·9 to more than 5·5) days. Thus, two patients still had a prolonged colonic transit time in spite of the irrigation. The defaecation score in these two patients was 29 and 230.

Large bowel function

Before the operation two patients suffered from incontinence to solid stools daily or several times per week. With antegrade colonic irrigation they had only a few minor episodes each month. Of the eight patients who had constipation before the operation, seven reported reduced time spent at defaecation, use of oral laxatives and need for digital evacuation of the rectum. Furthermore, they felt that their problems from constipation had been much or very much reduced. In one patient with constipation, antegrade irrigation sometimes failed and there was only minor symptomatic improvement with the treatment.

Overall satisfaction was very high in three patients, high in six and low in one patient. All patients were asked to compare bowel function before the operation and at follow-up using a scale in which zero was the worst possible and 100 ideal[10,13]. Before operation the median score was 3 (range 0–30), whereas at follow-up it was 85 (range 75–100). The patient with poor effect of the MACE failed to score bowel function at follow-up.

Discussion

This study deployed a new scintigraphic method for objective assessment of colorectal emptying following antegrade colonic irrigation and used a defaecation score as the primary endpoint. A scintigraphic study of normal defaecation in healthy subjects demonstrated a median defaecation score of about 100, indicating complete evacuation of the radioactive tracers located in the rectosigmoid[24]. In the present study the irrigation resulted in a median defaecation score of 350, indicating complete evacuation of radioactivity located in the rectosigmoid, the descending colon and the transverse colon plus 50 per cent emptying of radioactivity in the caecum and ascending colon. Thus, antegrade colonic irrigation induced a highly effective emptying of the large bowel even in patients with severe constipation. Accordingly, the colonic transit time was normalized in six of eight patients with constipation.

Using the dual-isotope technique, significant reflux to the ileum was found in the three patients with an ileal neoappendicostomy and in the patient with a caecal flap as a neoappendicostomy. However, the mild and transient side-effects in these patients were no different from those in patients with no reflux. In the six patients without reflux, the retained irrigation fluid extended throughout the large bowel, with most located in the left colon.

Studies have shown that colonic mass movements can be introduced by enemas[25], bisacodyl[26] and balloon distension[27]. Therefore, induced propulsive activity is most likely to add to the simple mechanical wash-out effect. Previous studies have suggested that the bowel wall of constipated patients is inert and less prone to respond to stimuli with propulsive activity in constipation[28–30]. Nevertheless, seven of eight constipated patients in the present study had significant emptying of the large bowel. All patients in this study had previously tried transanal retrograde colonic irrigation without success. Thus, bowel inertia is likely to be overcome by antegrade colonic irrigation.

There are comparatively few data concerning the use of the MACE in adults[9–13,17]. However, the functional results obtained in the present study are comparable to those of previous studies in children. During irrigation, mild side-effects are common but transient, and the treatment is generally well tolerated. Successful treatment leaves the patient with significant improvement in quality of life and with marked satisfaction with the procedure[10,13,17].

In conclusion, use of this scintigraphic method in patients with the MACE may guide the therapy towards more efficient treatment in individual patients and may help to identify physiological responses to different colonic irrigation regimens.

Acknowledgements

The study was supported by grants from Coloplast, Kokkedal, Denmark.

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Original article

Predictive value of internal anal sphincter thickness for diagnosis of rectal intussusception in patients with solitary rectal ulcer syndrome

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Background: The aim of this study was to determine any association between a thickened internal anal sphincter (IAS) on anal endosonography and high-grade rectal intussusception on evacuation proctography in patients with solitary rectal ulcer syndrome.

Methods: Anal endosonography was performed in 20 patients with solitary rectal ulcer syndrome and IAS thickness defined as normal or abnormal depending on age. Sphincter thickness was compared with the presence or absence of high-grade intussusception on subsequent evacuation proctography to determine any relationship between the two.

Results: Thirteen patients had an abnormally thick IAS, two of whom were unable to evacuate. Of the remaining 11 patients, ten showed high-grade intussusception (positive predictive value 91 per cent). Only three of seven patients with a normal IAS had high-grade intussusception (negative predictive value 57 per cent). Patients with a thick IAS were significantly more likely to have proctographic evidence of high-grade intussusception ($P = 0.047$).

Conclusion: Sonographic findings of a thick IAS are highly predictive for high-grade rectal intussusception in patients with solitary rectal ulcer syndrome.

Paper accepted 9 May 2002

British Journal of Surgery 2002, 89, 1281–1285

Introduction

Solitary rectal ulcer syndrome (SRUS) is an uncommon condition affecting young adults and is characterized clinically by rectal bleeding, mucus, tenesmus and difficult evacuation[1]. Proctoscopy reveals a spectrum of mucosal changes ranging from reddening, through polypoid thickening, to frank ulceration[2]. Abnormalities are anterior in most cases and biopsy characteristically shows collagenous replacement of the lamina propria and fibromuscular replacement of the mucosa[1]. Full-thickness rectal wall examination also reveals that the circular muscle is significantly thickened and condensed into bundles, features resembling high-pressure sphincter tissue[3]. Circular rectal wall muscle is continuous with the internal anal sphincter (IAS), which is also abnormally thickened in patients with SRUS when examined by anal endosonography[4]. Muscular rectal wall thickening may be a feature of recurrent rectal prolapse[3,5], which affects approximately 75 per cent of patients with SRUS; prolapse is confined to the rectum (intussusception) in approximately two-thirds, with the rest having complete rectal prolapse[6]. However, an association between intussusception and an abnormally thick IAS has not been proven in patients with SRUS. Sonographic and proctographic examinations of patients with proven SRUS have been reviewed in order to establish the relationship, if any, between IAS thickening and rectal prolapse.

Patients and methods

All patients with proven SRUS in whom anal endosonography and evacuation proctography had been performed were identified using both retrospective review and prospective data collection. No patient had undergone surgery for intussusception. Twenty patients, nine males and 11 females, of median age 33 (range 15–73) years, were identified. SRUS was confirmed by characteristic histological findings following rectal biopsy in all patients[1].

Anal endosonography was always performed first, using a Brüel and Kjær Medical 3535 scanner with an 1850 endoscopic probe (B&K Medical, Gentofte, Denmark). The first ten patients were scanned with a 7-MHz transducer and the remainder using an improved 10-MHz transducer (type 6004) with superior spatial resolution. The transducer was covered with a hard plastic sonolucent cone with an outer diameter of 1·7 cm. The 10-MHz transducer has a focal range of 5–45 mm, an axial resolution of less than 0·05 mm and a lateral resolution of 0·5–1 mm. The assembly was filled with degassed water for acoustic coupling, and covered with a lubricated condom for insertion. Patients were scanned in either the left lateral or prone position[7], and the endoprobe was inserted gently into the anus to the level of the anorectal verge. During slow withdrawal of the probe, images were taken at the following levels: high, mid and low anal canal. The high anal canal was defined as that level midway between the inferior border of the puborectalis and complete formation of the external sphincter ring anteriorly. Mid-canal level was defined by completion of the external sphincter ring anteriorly in combination with maximum IAS thickness. The low canal was defined as that level immediately caudal to the termination of the IAS, and comprised the subcutaneous external sphincter. Images were taken at two different magnifications and printed on laser film for subsequent analysis.

Evacuation proctography was subsequently performed using a simple standard technique[6]. Two glycerine suppositories were administered rectally and retained for 20 min; patients were then invited to empty the rectum in the toilet. With the patient in the left lateral position, 120 ml barium paste (E-Z paste®; E-Z-Em, Westbury, New York, USA) was instilled into the rectum using a bladder syringe. The patient was then seated upright on a specially designed commode and asked to empty the rectum as rapidly and completely as possible during lateral digital fluoroscopy with images acquired at one frame per second. Filming was intermittent if evacuation was delayed, prolonged, or both, so that the maximum screening time was kept to less than 60 s.

The anal endosonographic images were scanned electronically and images at mid-anal canal level were selected and stored on a personal computer. Using the centimetre scale reproduced on the sonographic image, an image analysis programme was calibrated for measurement (Scion Image 3b; Scion Corporation, Frederick, Maryland, USA), and measurements of IAS thickness were taken at 3 and 9 o'clock using the electronic callipers. All measurements were repeated three times by a single observer, and the mean was determined. Measurement reproducibility using this technique has been shown to be good[8].

Internal sphincter thickness was defined as normal or thicker than expected for age by a single observer who used data derived from a sonographic study of 150 asymptomatic female volunteers whose bowel habit had been characterized as normal using validated questionnaires[9]. Subjects from that study were divided into seven age groups, and a thick IAS for the purposes of the present study was defined as the mean IAS thickness (at mid-anal canal level) plus two standard deviations. The following seven age groupings and upper limit of normal IAS thickness were defined: age 20 years or less, 2·6 mm; age 21–30 years, 3·2 mm; age 31–40 years, 3·6 mm; age 41–50 years, 3·6 mm; age 51–60 years 3·4 mm; age 61–70 years, 3·7 mm; age 71 or over, 3·5 mm. Nine, 62, 43, 11, seven, 12 and six individuals, respectively, were used to define the seven age groups.

A second observer, unaware of the sonographic findings, reviewed the proctographic examinations. The presence or absence of rectal intussusception was noted and, if present, classified as high grade if the intussuscepting mucosa entered the anal canal or had a thickness greater than 3 mm. Low-grade intrarectal intussusception was considered a normal finding[10].

The relationship between the presence of high-grade intrarectal intussusception and IAS thickness was determined and categorical data were examined using Fisher's exact test.

Results

Median IAS thickness was 3·9 (range 2·9–8·6) mm. Taking age into account, 13 of the 20 patients studied had an abnormally thick IAS on endosonography (*Fig. 1*). Two of the 20 subjects were unable to evacuate any contrast, possibly masking intussusception, and were excluded from

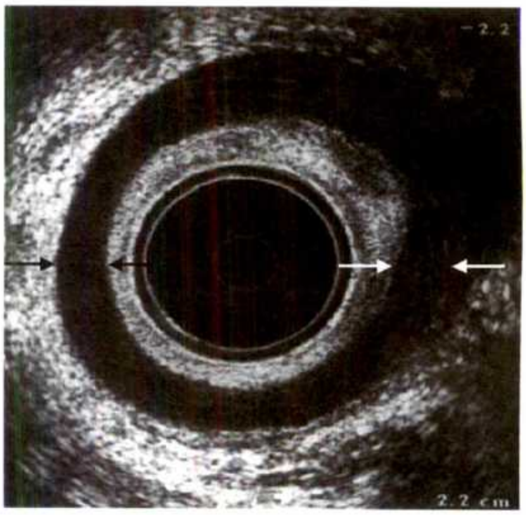
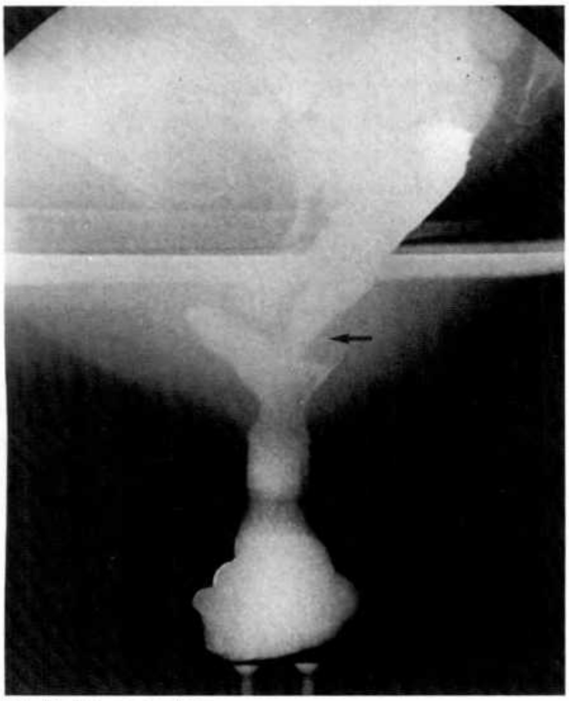
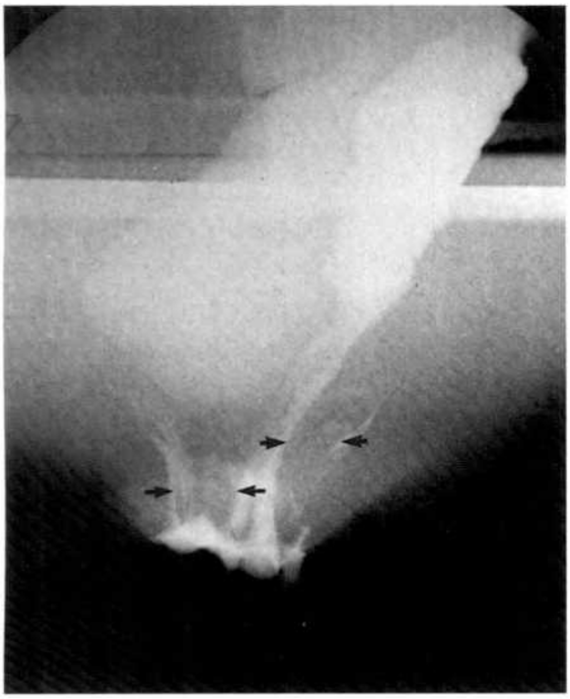


Fig. 1 Endoanal ultrasonogram at mid-canal level in a 54-year-old woman with solitary rectal ulcer syndrome. There is gross thickening of the internal anal sphincter (between arrows), which measured 7·3 mm



a During evacuation



b End of evacuation

Fig. 2 Evacuating proctography: lateral views during evacuation. **a** The intussuscepting mucosa descends from mid-rectal level, seen initially as a filling defect arising from the posterior rectal wall (arrow). **b** The intussuscepting mucosa (arrows) enters the anal canal at the end of evacuation, diagnosing high-grade intussusception

the subsequent analysis. Both of these had an abnormally thick IAS. Of the remaining 11 patients with a thick IAS, ten showed features of high-grade intussusception on evacuation proctography (*Fig. 2*). Overall, there were proctographic findings of high-grade rectal intussusception in 13 of the 18 patients who were able to evacuate, only three of whom had a normal IAS. Patients with a thick IAS had significantly more rectal intussusception than those whose sphincter was judged normal (ten of 11 *versus* three of seven patients; $P = 0{\cdot}047$, Fisher's exact test).

Excluding the two patients who were unable to evacuate, the finding of a thick IAS on anal endosonography had a positive predictive value of 91 per cent for proctographic features of high-grade intussusception. Of the seven patients with a sonographically normal IAS, three had proctographic evidence of high-grade rectal intussusception, giving a negative predictive value of 57 per cent.

Discussion

The purpose of this study was to identify the relationship, if any, between IAS thickness and rectal intussusception in a group of patients with histologically proven SRUS. Morphological internal sphincter abnormalities in SRUS were first documented in a study of 21 patients that showed the IAS, subepithelium and external anal sphincter were significantly thickened in these patients compared with age- and sex-matched controls[4]. The study used a 7-MHz transducer that was unable reliably to differentiate the longitudinal muscle and intersphincteric plane from the external sphincter, so that these two structures were incorporated into external sphincter measurements. Longitudinal muscle thickening in SRUS may help to explain the surprising finding of apparent external sphincter thickening in that study[3].

The reason for IAS thickening is unclear, but histological studies of rectal circular muscle, from which the IAS is derived, clearly demonstrate abnormal thickening in patients with SRUS[3]. Histologically, this is thought to be due to collagen deposition[3]. It has been suggested that mechanical stress due to intussusception and repetitive straining are the cause of this thickening[5]. Alternatively, it is postulated that the constant tenesmus typical of SRUS induces secondary hypertrophy of the muscularis propria[11]. Rectal wall thickening may be demonstrated *in vivo* using rectal ultrasonography; a study of 15 patients with SRUS found that the rectal muscularis propria was thicker than the normal upper limit of 2 mm in all cases[5]. Furthermore, this thickening was associated with rectal wall intussusception[5]. The present authors postulated that rectal intussusception would similarly be associated with IAS thickening.

This study has confirmed earlier observations that the IAS is abnormally thick in patients with SRUS. Thirteen of the 20 patients had a thicker IAS than would be expected for their age. Indeed, the thickest sphincter (8·6 mm) was found in the youngest patient, a boy aged 15 years. Furthermore, the study has also shown a significant association between this thickening and rectal intussusception, with a positive predictive value of 91 per cent. No patient in this group had complete rectal prolapse. Although rectal muscularis propria thickening and IAS thickening both seem to be associated with rectal intussusception, it is not known whether thickening of the latter is similarly due to excess collagen deposition; sphincter biopsy would be required to prove this. Furthermore, it remains unknown whether the IAS changes are secondary to mechanical strain, either directly on the sphincter or due to intussusception occurring in the rectal wall above. Indeed, a primary sphincter abnormality cannot be excluded. Alternatively, both intussusception and IAS thickening may be independently associated with some other, as yet unexplained, feature of the syndrome.

Data from a prospective sonographic study of asymptomatic women were used to define the upper limit of normal IAS thickness[9]. All had normal bowel habit confirmed using validated questionnaires. Limits were stratified for age because it is known that the normal IAS thickens with age[12]. A possible criticism is that only female control values were available. However, the authors considered that this was acceptable because previous sonographic studies have shown no difference between male and female IAS thickness[13,14]. Another potential criticism relates to the use of two different transducers, 7 and 10 MHz, although this seems unlikely to affect measurements of IAS thickness adversely because this muscle is so well delineated on ultrasonography, even when using the older transducer. In contrast, the external sphincter and longitudinal muscle are much better defined using the newer probe.

The present findings suggest that anal endosonography could be used as an alternative to evacuation proctography for the diagnosis of rectal intussusception in SRUS, thus perhaps avoiding irradiation in these patients, many of whom are women in their childbearing years. To date, evacuation proctography has been the 'gold standard' for diagnosis of intussusception in SRUS. A proctographic study[6] of 53 patients with proven SRUS found high-grade internal rectal intussusception in 36, and some studies have found an incidence of up to 94 per cent[15]. Approximately 50 per cent of patients with SRUS also have muscular incoordination of the pelvic floor, which can be diagnosed reliably by means of evacuation proctography when there is incomplete or prolonged emptying[16]; two of the patients in the present study failed to evacuate. When both prolapse and disorders of evacuation are considered, evacuation proctography demonstrates abnormalities in 75 per cent of patients with SRUS[6]. Rectal wall changes in SRUS are also demonstrable on barium enema, but the lack of functional information with respect to intussusception or muscular incoordination limits the usefulness of this technique[17].

Demonstration of intussusception and any coexisting functional disorder of evacuation is central to current management strategy for SRUS. Biofeedback may have a role in restoration of normal pelvic floor function, especially where behavioural disorder is dominant[18]. Conversely, surgery is likely to be helpful only when there is significant intussusception or complete rectal prolapse and, even then, a consensus is emerging that it should be reserved for selected patients with severe symptoms only. A proctographic study of 23 patients with SRUS found that rectopexy successfully treated prolapse in all but one patient, but 16 remained symptomatic[19]. Most authors would agree that the aetiology of SRUS is multifactorial and that management is consequently difficult.

In summary, this study has demonstrated that excessive IAS thickening in patients with SRUS is significantly associated with high-grade rectal intussusception. Endosonography may be used to identify patients suffering from intussusception, but the cause of these alterations in IAS morphology remains unknown.

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Original article

Pelvic exenteration for advanced colorectal cancer with reconstruction of urinary and sphincter functions

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Background: Total pelvic exenteration (TPE) for the treatment of advanced colorectal cancer usually involves a double stoma for faecal and urinary excretion, which reduces patient quality of life. In this study, a stomaless reconstruction method for patients normally requiring TPE was evaluated.

Methods: Five patients underwent stomaless TPE. After removal of the tumour with an adequate surgical margin, the urethra was transected at the urogenital diaphragm and the rectum at the anal canal. An ileal neobladder was constructed and coloanal anastomosis was performed. The major omentum was used to construct a septum between the anastomoses. A transgastric ileus tube was used as an intestinal stent to prevent ileus.

Results: All patients were alive 12–39 months after operation. Faecal continence was preserved in four patients whose diverting colostomies were closed. All five patients were able to void urine spontaneously, with daytime continence. All but one, in whom cancer recurred, were mobile in the community.

Conclusion: Stomaless TPE may be considered for locally advanced colorectal cancers that invade the genitourinary organs, provided that neither the anal canal nor the urogenital diaphragm is affected.

Paper accepted 11 June 2002

British Journal of Surgery 2002, **89**, 1286–1289

Introduction

Total pelvic exenteration (TPE) is an aggressive surgical procedure used in the treatment of locally advanced colorectal cancer. The procedure is employed when preoperative examination indicates extensive invasion by tumours affecting the prostate, seminal vesicle and the trigone of the urinary bladder, requiring resection with an adequate surgical margin[1]. TPE is an invasive and formidable procedure with high associated mortality and morbidity rates[2,3]. Diversion of urinary and anal functions is frequently selected in patients with a combined sigmoid colostomy and ileal conduit, in order to minimize postoperative complications[4].

Recent advances in sphincter-saving operations for distal rectal cancer have allowed coloanal anastomoses to be performed without adverse effects on outcome[5,6] and orthotopic neobladder construction has become a standard procedure following cystoproctatectomy for invasive bladder cancer[7,8]. A combination of these advances may improve postoperative quality of life in patients with advanced rectal cancer who require TPE, provided that both the urogenic diaphragm and anal sphincter can be preserved. Use of these procedures to achieve stomaless TPE in five patients diagnosed with advanced primary or recurrent colorectal cancer is reported.

Patients and methods

Patients

The patient group comprised five men (aged 51–67 years) with advanced rectal or sigmoid colonic cancer. Three complained of pneumaturia at the first consultation. Preoperative tumour staging was conducted using barium enema, colonoscopy, endoscopic ultrasonography (EUS), computed tomography (CT), transabdominal echography and magnetic resonance imaging (MRI). Positron emission tomography (PET) was performed before operation to rule out multiple metastatic disease in one patient who presented with a locally recurrent lesion. All tumours had invaded the prostate, seminal vesicles or both. Disease stage and the potential morbidity of stomaless TPE were explained fully, and all patients expressed a strong desire to proceed. The operations were performed between 1998 and 2001.

Operative technique

Laparotomy was performed using a midline incision. The left colon was mobilized and the inferior mesenteric artery was transected. Para-aortic lymphadenectomy was performed as far as the pelvic side-wall, where the lateral muscles, presacral venous plexus and sciatic nerves were exposed. The obturator nerves were preserved, but the hypogastric plexuses were resected. Both internal iliac arteries were ligated. Following transection of the urethra at the level of the urogenital diaphragm, the rectum was divided at the top of the anal canal. *En bloc* resection was performed. Following stapled coloanal anastomosis, a flap of greater omentum based on the left gastroepiploic artery was introduced and fixed at the bottom of the pelvis in the last three patients, creating a septum between two closely located anastomoses (the already constructed coloanal anastomosis and the imminent neobladder–urethral anastomosis). The ileal neobladder was constructed according to the methods of either Hautmann *et al.*[9] or Studer and colleagues[10]. A long ileus tube was inserted via the stomach to allow decompression of the anastomosis but also to function as an intestinal stent for the prevention of postoperative obstruction. A transverse loop colostomy was constructed in three patients. The final appearance of the reconstruction is illustrated in *Fig. 1*.

Results

In all patients, large immobile tumours were present in the pelvis. Gradual dissection, from every direction, was necessary for removal of the tumours. The operating time ranged from 12 to 13·5 h, and blood loss from 1300 to 6700 (mean 3940) ml.

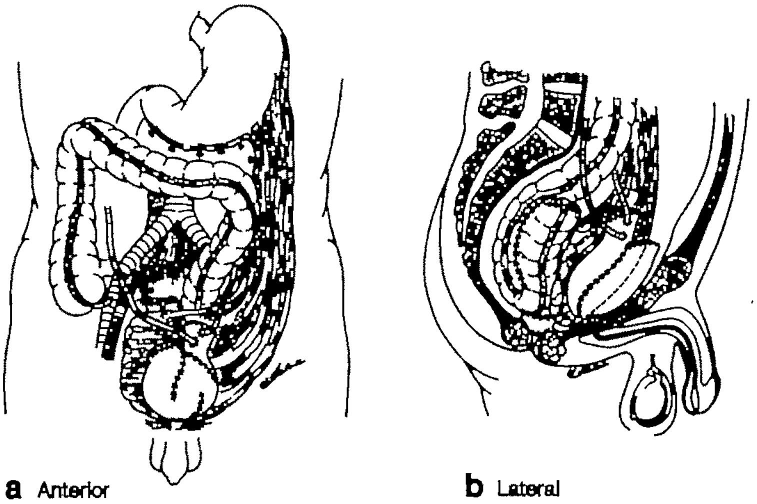
Histopathological diagnosis showed direct infiltration of the prostate, seminal vesicle or trigone of the bladder in two patients. In the remaining three patients, inflammation and abscess formation at the invasion front were noted, together with some scattered cancer nests adjacent to these organs.

Early complications

Two major perioperative complications were encountered. In one patient a fistula developed between the coloanal and neobladder–urethral anastomoses 2 weeks after operation. A transverse colostomy was created for diversion and the patient was discharged after an additional 6 weeks. In response to this outcome, the major omentum was wrapped around the coloanal anastomosis and fixed to the pelvic wall in the following three patients. The second complication involved leakage at the coloanal anastomosis. This problem resolved within 1 month without additional treatment. No other major perioperative complications were observed.

Functional outcome

At the time of discharge, all five patients could void urine spontaneously. At the routine check-up 2 months after discharge, the cystometric capacity ranged from a minimum of 300 to 500 ml. The postvoiding volume ranged from 20 to 90 ml, and was less than 50 ml in four of the five patients. Only one patient used a pad at night for occasional nocturnal incontinence. This patient had required self-catheterization before operation owing to denervation



a Anterior

b Lateral

Fig. 1 a Anterior and b lateral images of a novel stomaless reconstruction after total pelvic exenteration. The major omentum is introduced into the pelvis to construct a septum between the coloanal and neobladder–urethral anastomoses caused by lateral lymph node dissection in the primary operation, and so urinary function had improved compared with preoperative status. Daytime urinary continence was preserved in all patients. Throughout the follow-up period, no major adverse effects associated with the neobladder have been noted.

Disease recurred in one patient before closure of the diverting transverse colostomy and chemotherapy was instituted. The remaining patients could delay defaecation for more than 15 min, and the frequency of defaecation was less than five per day. Manometric assessment, performed 6 and 12 months after closure of the stoma, indicated no substantial differences in function compared with that following standard low anterior resection. The functional anal canal length was at least 3·0 cm, and resting anal canal pressure ranged from 40 to 80 mmHg. Two patients, however, have complained of occasional multiple evacuations within 1 h to empty the neorectum, as is often seen in patients treated with low anterior resection[11]. Throughout the follow-up period, no patient has complained of frequent abdominal pain, nausea, bloody stool, diarrhoea, heartburn or difficulty in eating, which represent the major contributors to impaired quality of life[12].

Prognosis

Although no patient received preoperative adjuvant therapy, oral 5-fluorouracil derivatives were administered after operation to all patients when laboratory data had returned to normal. The duration of postoperative hospital stay was less than 5 weeks in four of the five patients, which was slightly shorter than that following conventional TPE with a double stoma (mean 38 days) for this department. One patient with failure of the anastomosis was in hospital for 8 weeks after operation.

All patients were alive at the time of writing. Postoperative follow-up ranged from 12 to 39 months. In one patient, intra-abdominal disseminated disease and lung metastasis were noted 10 months after operation, and systemic chemotherapy was current at time of writing, with the patient confined to home. Three of the patients had returned to work within 3 months of final discharge. One patient retired from work, but remains mobile and active in the community.

Discussion

TPE for advanced rectal cancer is a formidable intervention with high morbidity and mortality rates[2,3]. It has therefore been recommended as suitable only for experienced surgeons at specialized centres[13]. However, the morbidity rate has decreased as the surgical technique has been standardized[14] and improvements in functional outcome following this procedure are worthy of attention.

In the stomaless TPE described, the autonomic nerves branching from the pelvic plexus and the hypogastric nerve are totally sacrificed. As a result, the physiological reflex through the internal urinary sphincter is lost. However, patients can void urine spontaneously and daytime continence is preserved. Anal function is similar to that obtained by conventional low anterior resection. Recovery of function is probably achieved because somatic sensation and contraction of the external sphincters remains intact through cerebral control via the pudendal nerve. In this context, occasional nocturnal incontinence is to be expected.

Of the five men reported in this series, three returned to their previous employment within 3 months after final discharge from hospital, and one patient retired from work but is mobile in the community; only one patient remains confined to home owing to recurrent disease. In comparison, of 38 men who underwent conventional TPE with a double stoma and were discharged previously, only two returned to their former employment and 12 retired from work but are mobile in the community; the remaining majority are confined to home because of the care required for the double stoma or owing to chronic infection in the pelvic cavity or abdominal wound[14]. Postoperative quality of life in patients receiving stomaless TPE is therefore substantially improved compared with that after conventional TPE.

Two early postoperative complications were associated with this procedure. One was the formation of a fistula between the coloanal and pouch–urethral anastomoses, which necessitated the construction of a diverting stoma. To address this problem, a diverting stoma was constructed in the following three patients, and the major omentum was introduced into the pelvis to construct a septum between the anastomoses. With this precaution, early anastomotic failure at the coloanal anastomosis occurred in one patient; this healed within 1 month, with no additional treatment. Use of the major omentum to construct a septum between the two anastomoses is extremely important for the safe performance of stomaless TPE. It is also helpful in reducing dead space in the pelvic cavity, and should therefore reduce the risk of postoperative pelvic infection commonly seen in conventional TPE[15].

Another possible complication relates to the fact that stomaless TPE is accompanied by multiple organ mobilization. If postoperative ileus should occur, reoperation would be difficult. Since 1996, a transgastric ileus tube has been inserted and introduced to the terminal ileum at the time of operation. Of 61 patients who previously underwent TPE, a transgastric ileus tube was inserted in the last 23. No postoperative ileus has been noted in these patients, whereas nine of the 38 earlier patients suffered an episode of perioperative ileus and three required reoperation. A transgastric ileus tube, introduced up to the terminal ileum, functions as an intestinal stent and helps to prevent mechanical ileus.

Stomaless reconstruction after TPE has been shown to be feasible, producing an acceptable outcome for both urinary and defaecatory functions. The technique may be an option for patients whose lesions can be removed curatively, who wish to avoid a stoma, and who accept the risk of possible side-effects associated with the surgical procedure. To identify suitable patients for this procedure, thorough preoperative examination is essential to determine tumour stage. In addition to conventional modalities including CT, MRI or EUS, PET has proved effective in evaluating tumour location in patients with locally recurrent lesions[16]. When available, whole-body PET[17] can provide extremely useful information for determining tumour stage and indications for this procedure. So far the technique has been applied to selected patients presenting with single tumours that occupy limited areas of the pelvis and no large lymph node metastases. Technically, more than 50 per cent of patients who have undergone TPE with a double stoma in this department would have been candidates for this procedure.

The merits of stomaless TPE are substantially reduced by early recurrence, as seen in one patient in the present series. If patients with more advanced tumours are to be treated with this procedure, neoadjuvant radiotherapy to facilitate downstaging of the tumour will be necessary. Stomaless TPE is contraindicated for patients with substantial lymph node involvement or multifocal recurrent disease who have a high risk of local recurrence and in whom subsequent radiotherapy may be required. The conventional reconstruction method using a double stoma is the first choice for such patients. Once stomaless TPE has been selected, both separation of the two anastomoses by fixing the major omentum into the pelvis and introduction of a transgastric ileus tube stent are considered to be of the greatest importance to a safe outcome.

Acknowledgements

This work was supported partially by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education (no. 11671149). The authors thank Dr T. Igarashi for advice on technical matters.

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Intraoperative scrape cytology of the sentinel lymph node in patients with breast cancer

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Background: Intraoperative examination of the sentinel lymph node (SLN) may detect metastatic disease, allowing immediate axillary lymph node dissection and therefore avoiding the need for reoperation. The aim of this study was to evaluate the accuracy of scrape cytology of the SLN in patients with early breast cancer.

Methods: Sentinel node biopsy was performed in 148 patients with clinical T1–2 N0 breast cancer. After harvesting, the SLN was bisected and cells from both halves were scraped with a scalpel blade on to a slide and stained with a Papanicolaou and Giemsa stain. Scrape cytology results were compared with the results of paraffin sections stained with haematoxylin and eosin and with immunohistochemistry.

Results: The intraoperative diagnosis was correct in 126 patients (85 per cent). Sensitivity and specificity were 67 and 98 per cent respectively; positive and negative predictive values were 95 and 81 per cent.

Conclusion: Scrape cytology is a useful method for intraoperative evaluation of the SLN in patients with breast cancer.

Paper accepted 3 May 2002

British Journal of Surgery 2002, **89**, 1290–1293

Introduction

The histological status of the axillary lymph nodes remains one of the most important prognostic indicators in patients with breast cancer[1]. The sentinel lymph node (SLN) has proved to be a reliable predictor of the histological status of the remaining axillary lymph nodes[2–6]. SLN biopsy has the advantage of decreased postoperative morbidity compared with complete axillary lymph node dissection (ALND). A disadvantage is the need for reoperation if metastatic disease is found in the SLN.

Intraoperative examination of the SLN may detect metastatic disease, allowing immediate ALND. Two techniques already in use for intraoperative examination are frozen sectioning and imprint cytology. Frozen sectioning offers visualization of architecture of the lymph node, but is tissue consuming and causes artefacts to definitive pathology[7,8]. Imprint cytology offers cytological detail and preserves the entire lymph node for definitive histopathology. Disadvantages include the small number of cells sampled and the higher chance of indeterminate results caused by atypical cells[8,9].

Scrape cytology of the SLN is an alternative that combines the tissue preservation of cytology with the advantage of a larger number of cells for examination[8,10,11].

The aim of this study was to ascertain the value of intraoperative scrape cytology in determining the histological status of the SLN in patients with early breast cancer.

Patients and methods

Between June 2000 and July 2001, 168 patients had a SLN biopsy for clinical stage T1–2 N0 breast cancer. In three patients the SLN procedure was not successful and an ALND was performed in the same session. In 17 patients the SLNs were examined only after operation. In the remaining 148 patients the SLN was examined during the operation by scrape cytology. The median age of these patients was 56 (range 27–95) years. The pathological median tumour size was 16 (range 0–80) mm. The tumour stage was Tis in three patients (2 per cent), T1 in 86 patients (58 per cent), T2 in 51 patients (34 per cent), T3 in one (1 per cent) and T0 in seven patients (5 per cent). In 26 patients an excision biopsy was performed before the SLN procedure.

Of the 148 patients, 109 (74 per cent) had invasive ductal cancer (IDC), three (2 per cent) had *in situ* ductal cancer, 18 (12 per cent) had invasive lobular cancer (ILC) and the remaining 18 (12 per cent) had intracystic papillary cancer, tubular cancer, metaplastic cancer, Paget's disease, medullary cancer or fibroadenoma.

SLN biopsy was performed according to Dutch guidelines using technetium-99m nanocolloid as a radioactive tracer and Patent blue dye (Bleu patente V; Guerbet, Aulnay-sous-Bois, France) for lymphatic mapping; both were injected around the tumour or around the scar when there had been previous excision biopsy[3,12,13]. At operation a maximum of three sentinel nodes was sent to the pathology department for examination by scrape cytology. If more SLNs were identified, only the most suspicious were examined by scrape cytology. Each SLN was bisected, after which cells from both sides were scraped with a scalpel blade on to a slide. The material was fixed in 96 per cent alcohol or air dried and subsequently stained with a Giemsa and Papanicolaou stain. The slides were first screened by a cytological technician and then reviewed by an experienced pathologist. The whole procedure, including communication of the results, took about 20 min.

The remaining node halves and other sentinel nodes were examined routinely by embedding in paraffin, step sectioning at 500-μm intervals at three levels, and staining with haematoxylin and eosin. If the SLN was negative on haematoxylin and eosin staining, immunohistochemical staining at the three levels was performed. Cam5·2 is a monoclonal antibody directed against cytokeratin 8 localized in the cytoplasm of the tumour cells (Becton Dickinson, San Jose, California, USA).

Scrape cytology results were compared with routine and immunohistochemical staining. Diagnostic accuracy, sensitivity and specificity, and positive and negative predictive values were calculated.

Results

A total of 268 SLNs were biopsied from 148 patients, a median of 2 (range 1–5) per patient. Sixty patients (41 per cent) were found to have metastatic involvement.

When evaluating the data per patient, 42 patients had at least one positive SLN with scrape cytology. In two patients the SLN was positive on scrape cytology and negative on histopathology. Both of these patients had a T1 tumour and IDC. In 40 patients with positive histopathology, scrape cytology of at least one SLN was positive (sensitivity 67 per cent). The specificity of scrape cytology of the SLN was 98 per cent. The positive and negative predictive values were 95 and 81 per cent respectively. The overall accuracy of the scrape cytology procedure per patient was 85 per cent. Results per node were not calculated, because the consequences of scrape cytology are taken at a patient level.

In 20 patients scrape cytology gave a false-negative result. This occurred in 14 patients with IDC (13 per cent of all patients with IDC), four patients with ILC (22 per cent of all patients with ILC), and two patients with medullary and tubular cancer (11 per cent of all patients with other types of cancer). Ten of 20 patients with false-negative scrape cytology results actually had micrometastasis in the SLN (defined as a focus of 2 mm or less), as did seven of the 40 patients with positive scrape cytology and histopathology findings. At subsequent ALND only four of 20 patients had additional positive nodes: one extra, twice and two extra, twice. The mean number of positive nodes found with ALND was 0·2 for the group with negative scrape cytology and positive histopathology, compared with 2·5 for the group with positive scrape cytology and histopathology.

Micrometastases were identified in 17 (28 per cent) of 60 patients with metastatic disease[14]. Seven of these were found with scrape cytology and confirmed in the haematoxylin and eosin-stained slide. In three patients, metastatic disease was discovered only by immunohistochemistry.

Discussion

Several authors have already reported the results of intraoperative frozen sectioning and imprint cytology of the SLN in patients with breast cancer. The mean accuracy for frozen sectioning in the literature is 89 per cent, with a range from 83 to 96 per cent[2,3,7,8,14,15]. The mean accuracy for imprint cytology ranges from 78 to 98 per cent, with a mean of 91 per cent[15–18]. The results of the various studies are difficult to compare. They might be influenced by the lack of additional immunohistochemical staining in three of ten studies and routine ALND in six of ten studies[2,6,9,15,17,18]. Only two authors compared imprint cytology and frozen sectioning; they came to different conclusions[15,16] (*Table 1*). In the present study the accuracy of scrape cytology per patient was 85 per cent.

The distribution of metastases throughout the SLN is not uniform. At least 30 per cent of the metastases in a SLN might be missed with intraoperative examination by scrape cytology after bisection of the SLN. In the present study metastatic disease was diagnosed during operation in 40 patients (67 per cent), which corresponds with the findings of other authors. Two false-positive scrape cytology results were found, both in patients with a T1 tumour and IDC. In both patients this was caused by an interpretation error in the early phase of the trial[19].

Table 1 Review of publications concerning intraoperative sentinel lymph node examination

Reference	Year	Technique	Accuracy (%)	No. of patients	Routine ALND	IHC
Motomura *et al.*[15]	2000	FS	88	101	+	+
		IC	96	101	+	+
Veronesi *et al.*[2]	1997	FS	83	107	+	+
Flett *et al.*[6]	1998	FS	95	56	+	−
Ratanawichitrasin *et al.*[17]	1999	IC	98	55	+	−
Rubio *et al.*[9]	1998	IC	98	55	+	−
Cserni[18]	2001	IC	78	60	+	+
Van Diest *et al.*[16]	1999	FS	96	54	−	+
		IC	82	54	−	+
Weiser *et al.*[22]	2000	FS	89	890	−	+
Turner and Giuliano[8]	1998	FS	93	225	−	+
Rahusen *et al.*[3]	2000	FS	84	100	−	+
Present series	2002	SC	85	148	−	+

FS, frozen sectioning; IC, imprint cytology; SC, scrape cytology; ALND, axillary lymph node dissection; IHC, immunohistochemical staining

In the present study, 28 per cent of the patients with metastatic disease had micrometastases in the SLN, similar to the results of other authors, who describe incidences ranging from 12 to 51 per cent[5,8,9,19–21]. The percentage of micrometastases found during operation by frozen sectioning or imprint cytology in the literature varies widely from 17 to 100 per cent[8,9,22]. Rubio *et al.*[9] reported micrometastases in only 12 per cent of all positive SLNs, all of which were found by imprint cytology. These results may have been influenced by the lack of additional immunohistochemical staining and routine ALND, which may influence a pathologist in describing 'suspicious' slides[8,9]. In the present study scrape cytology revealed seven of 17 cases of micrometastatic disease during operation. Half of all false-negative results were due to micrometastatic disease.

Finding a metastasis depends on its distribution and site in the SLN. The results of scrape cytology might be improved by making further cross-sections of the SLN (mean size 11 mm)[15], although this will have limitations of thickness of the slide (3–4 mm). This procedure would be time consuming and might destroy the morphology of the SLN. Immunohistochemistry takes too long for an intraoperative diagnosis.

Scrape cytology yielded results similar to those of imprint cytology and frozen sectioning of the sentinel node, and could be used for intraoperative analysis of the SLN in patients with breast cancer.

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Incidence of nodes in completion mastectomy specimens following breast conservation and axillary clearance

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Paper accepted 12 May 2002

Introduction

Axillary node clearance is the 'gold standard' surgical management of the axilla for women with invasive breast cancer[1]. This procedure provides both information for further treatment decisions and treats any disease present in the axilla. Axillary clearance is an operation with clearly defined anatomical margins with the exception of the inferior limit of dissection[2]. This is not a problem when the axillary clearance is combined with a mastectomy as the operation is performed *en bloc*. When axillary clearance is combined with breast conservation, the surgeon must decide on the inferior border of the axillary dissection, and any nodes lying below this will be left behind.

Sentinel node biopsy has recently highlighted the possibility of missing low-lying nodes. They are often lower in level 1 than might be expected, and below the inferior limit of an axillary clearance. The question is whether clinically important nodes may be left in the low axilla following axillary clearance, when combined with breast-conserving surgery.

The majority women who have breast conservation require no further surgery, so it is not possible to determine whether nodes have been left. A few women require completion mastectomy for adverse histological features such as multifocal disease or extensive carcinoma *in situ*. The completion mastectomy specimen will contain any nodes left *in situ* following the original axillary clearance and breast conservation.

The aim of this study was to determine the frequency with which nodes are retained in the low axilla following axillary clearance and breast conservation.

Patients and methods

The study included women with histologically confirmed invasive breast cancer who had a completion mastectomy after breast conservation and formal axillary node clearance of at least level 1. Patients with axillary sampling were excluded from the study. A study group was identified from the operating theatre databases of the Cardiff breast team. The entire database was searched, from its inception in January 1996 to February 2000.

Pathology reports of the initial axillary clearance and the subsequent completion mastectomy were obtained for the study population. The axillary clearance report was examined to determine the number of nodes found and their histological status. The completion mastectomy report was then examined to determine whether any nodes had been found in the specimen. As the study was retrospective, the completion mastectomy specimens were examined according to the routine procedures of the pathology department.

Results

Fifty-four women met the inclusion criteria; 30 (56 per cent) were node positive and 24 (44 per cent) were node negative. Eleven women (20 per cent) had lymph nodes documented in the completion mastectomy pathology report. Of the 30 node-positive women, seven had nodes at completion mastectomy, compared with four of the 24 node-negative patients ($P = 0{\cdot}55$, χ^2 test).

The mean number of nodes in the original axillary clearance was 12·5 for the whole study group, 12·0 for the 11 women who had nodes found at completion mastectomy and 12·6 for the 43 women with no nodes found in the completion mastectomy specimen ($P = 0{\cdot}69$, Student's t test). The mean number of nodes found in the 11 patients at completion mastectomy was 1·9 (range 1–5).

Of the 11 patients with nodes present at completion mastectomy, two had nodes involved by metastatic tumour. In one this was the only node found in the completion mastectomy specimen; in the other woman three of five nodes were positive. These women both had a positive axillary clearance, with one of 12 and five of six nodes positive respectively. Therefore neither patient was upstaged.

Discussion

A significant minority of women (20 per cent) in this study had nodes found in the low axilla or axillary tail of the breast. The nodes contained metastases in two of the 11 women. Because of the retrospective nature of this study it was not possible to determine the exact site of the nodes that were retrieved.

The proportion of node-positive tumours in this study was higher than expected for a group of women undergoing primary breast cancer surgery[3]. This is probably because women undergoing completion mastectomy were more likely to have relatively large, high-grade or multifocal primary tumours. However, the axillary clearances appeared to be comparable across the study population, as there was no significant difference in the number of nodes in the original clearance whether or not nodes were found in the completion mastectomy specimen.

The true incidence of retained nodes may be even higher. This was a retrospective study; the objectives of histological assessment for an axillary clearance, to determine the number and status of lymph nodes, differed from those for a completion mastectomy, which concentrated on determination of residual primary tumour or multifocal disease. Searching for lymph nodes in the axillary tail of the specimen was a secondary concern. A prospective study with strict protocols for pathological examination might reveal a higher incidence of nodes in the completion mastectomy specimen.

This study suggests that positive nodes may be left in the axilla following axillary clearance when combined with breast conservation. This has two important implications. First, because axillary clearance is the standard in treatment of the axilla, women do not receive any further axillary treatment. Therefore, a higher rate of axillary recurrence might be expected in patients who have had breast conservation. This does not seem to be the case[4]. This could be explained by the breast radiotherapy now given to most women who have breast conservation; the relevant nodes are low in the axilla or in the axillary tail in the breast, and fall within the radiotherapy field. Such nodes may contribute to the high local recurrence rate seen in patients treated by breast conservation without radiotherapy[5].

The second concern is that women may be being understaged. Some women, in whom all nodes in the axillary clearance were negative and who were therefore regarded as 'node negative', may have had one or more positive nodes in the low axilla. This is relevant because node status is an important component in selecting adjuvant treatment. No patient was upstaged in this study but one woman with a positive node in the completion mastectomy specimen had only one positive node in the axillary clearance specimen. A larger prospective study is needed to establish the true risk of understaging and the exact location of the nodes.

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Role of magnetic resonance imaging in the diagnosis and single-stage surgical resection of invasive lobular carcinoma of the breast

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Background: Conventional imaging with mammography and ultrasonography has a low sensitivity for diagnosis and a tendency to underestimate the extent of invasive lobular carcinoma (ILC) of the breast. The aim was to determine whether magnetic resonance imaging (MRI) had any advantages for the characterization of ILC.

Methods: Twenty patients with histologically proven ILC underwent preoperative imaging with MRI. MRI was performed to aid detection of malignancy in six patients with a clinically suspicious presentation but normal or indeterminate imaging on mammography and ultrasonography. In 14 patients MRI was performed to determine tumour extent.

Results: MRI accurately identified malignancy in five of six patients with normal or indeterminate conventional imaging. In seven of 14 patients in whom MRI was performed to determine tumour extent, it provided significant additional information. These included four patients in whom conventional imaging grossly underestimated tumour size, two patients in whom MRI identified an unsuspected contralateral breast tumour and one patient in whom MRI predicted tumour invasion of the pectoral muscle. The correlation between tumour size on histological examination was better with MRI ($r = 0{\cdot}967$) than with mammography ($r = 0{\cdot}663$) and ultrasonography ($r = 0{\cdot}673$).

Conclusion: MRI can provide considerable additional information in the detection and characterization of ILC.

Presented to the Association of Surgeons of Great Britain and Ireland, Birmingham, UK, May 2001, and to the Seventh Nottingham International Breast Cancer Conference, Nottingham, UK, September 2001
Paper accepted 11 June 2002
British Journal of Surgery 2002, **89**, 1296–1301

Introduction

Invasive lobular carcinomas (ILCs) are diffusely infiltrative tumours composed of linear arrays of homogeneous, small, round and regular cells, and represent around 10 per cent of all breast cancers[1]. A surrounding desmoplastic reaction is less evident in ILC than invasive ductal carcinoma (IDC). Owing to the diffuse growth pattern of cellular infiltration and the lack of a desmoplastic reaction, ILCs may fail to produce a discrete dominant mass and are therefore difficult to define on palpation[2,3]. Similarly, these biological characteristics make them relatively radiolucent, often causing minimal or no mammographic abnormality[4,5]. Their relative hypocellularity and the small, regular nature of the cells means that fine-needle aspiration cytology (FNAC) is reported as inadequate (C1) or benign (C2) in more than one-third of cases of ILC[6]. ILCs therefore often present a diagnostic challenge even with thorough triple assessment. This probably explains why they are of a larger size at diagnosis than IDCs[3] and comprise a greater proportion of cancers in which a delay in diagnosis has occurred.

Tumour size is estimated by palpation, assisted by mammography and ultrasonography, when planning surgical excision. Tumours greater than 40 mm in diameter are generally considered less suitable for breast-conserving surgery[7]. The imprecise palpable and radiological features of ILC cause difficulty in determining the extent of the cancer. Previous studies have shown that both mammography[8–10] and ultrasonography[10] tend to underestimate the size of an ILC compared with its histological size. Consequently ILCs are associated with a high risk of involvement of the surgical margins when breast-conserving surgery is attempted[8,9,11,12], so multiple surgical procedures are required to achieve adequate surgical clearance. Contrast-enhanced magnetic resonance imaging (MRI) of the breast has a high degree of sensitivity for the diagnosis of breast cancer, with most studies reporting a sensitivity in excess of 90 per cent[13–17]. There is also evidence of improved preoperative determination of breast cancer extent with MRI compared with conventional imaging[18–21].

The MRI findings of 20 patients with ILC were analysed to determine whether MRI can provide clinically important information on the detection and extent of ILC that cannot be obtained with conventional imaging methods, such as mammography and ultrasonography, and thereby facilitate single-stage surgery for these tumours. The size of the tumour on mammography, ultrasonography and MRI was correlated with the size on detailed histopathological examination.

Patients and methods

The patients were selected from a breast MRI database. All patients who underwent preoperative MRI between June 1998 and December 2000 and who had histologically proven ILC were selected ($n = 20$). The age range was 39–78 (median 61) years.

The decision to perform MRI was taken in the context of a multidisciplinary meeting following conventional triple assessment consisting of clinical examination, imaging with mammography and ultrasonography, and FNAC or core biopsy in patients with a palpable lump and/or an abnormality on imaging. The indications for performing MRI were: patients with a known breast cancer measuring less than 40 mm on conventional imaging and considered suitable for breast-conserving surgery ($n = 14$), and patients with clinical suspicion of breast cancer but a non-diagnostic triple assessment ($n = 6$).

The clinical presentation of the six patients with a clinically suspicious abnormality included: distortion of the breast with an underlying palpable mass, mammography and ultrasonography normal but FNAC or core biopsy showing malignancy ($n = 2$); distortion of the breast with no underlying palpable abnormality and mammography and ultrasonography normal ($n = 2$); metastatic adenocarcinoma in an axillary lymph node but no palpable abnormality within the breast and normal mammography and ultrasonography ($n = 1$); and a clinically indeterminate lump with normal mammography and ultrasonography and benign FNAC ($n = 1$).

MRI was not performed in patients with tumours greater than 40 mm on imaging as they required a mastectomy and MRI would not have affected the choice of surgical treatment.

Mammography and ultrasonography were performed by one of two specialist breast radiologists and were reported as R1–R5 (R1, no abnormality; R2, benign; R3, indeterminate; R4, suspicious; R5, malignant). The findings on MRI were reported by a specialist breast radiologist, who was aware of the findings of the triple assessment. This reflects clinical practice, where MRI is likely to be used as an adjunct to rather than a replacement for conventional triple assessment. The cytology and histology were reported by specialist breast histopathologists. The cytology was reported on a scale of C1–C5 as for the radiology. A classification of suspicious or malignant was taken as positive for the purposes of calculating the sensitivity of each of these investigations. All patients had a preoperative diagnosis of malignancy with FNAC and/or core biopsy before definitive surgery.

The decision to perform mastectomy or breast-conserving surgery was taken by a consultant breast surgeon after considering the findings of triple assessment and MRI. The size and extent of the tumour on MRI was used to plan surgical treatment. Indications for performing mastectomy were: tumours greater than 40 mm in size, multicentric tumours, tumours located centrally within the breast and tumours invading the pectoral muscles.

The extent of the tumour on conventional imaging (mammography and ultrasonography) and MRI was correlated with the findings of histopathological examination of the surgically resected specimens. For the purposes of statistical analysis the maximum diameter of the tumour determined by each of the imaging modalities was correlated with the maximum diameter of the tumour on histological examination in 17 patients in whom an exact assessment of size was possible. In two patients an accurate assessment of the tumour size was difficult to make because of the diffuse multicentric nature of the cancer and in one patient imaging with all modalities failed to identify tumour.

Dynamic contrast-enhanced magnetic resonance imaging

MRI was performed with a 1·5-T whole-body scanner (Philips Magnet, Philips Medical Systems, Eindhoven, The Netherlands) using a double breast surface coil. The dynamic contrast-enhanced study consisted of a series of T1-weighted two-dimensional gradient echo dynamic images, each with 25 sections of 4 mm thickness in the axial plane. Two sequences of imaging were obtained before the administration of dimeglumine gadopentate (Magnevist®; Schering, Berlin, Germany) as contrast at a dose of 0·1 mmol per kg body-weight, followed by ten sequences after administration of contrast. Each dynamic scan takes 36 s and the total scanning time for the sequence was approximately 7 min. All the dynamic images were subtracted and enhancement curves were drawn of regions of interest. A specialist radiologist interpreted the images, based on morphology, enhancement patterns and volumetric analysis, using Easyvision software (Philips Medical Systems). The cost of each MRI scan, including use of dye and other resources for performing and reporting the scan, was estimated to be approximately £400.

Statistical analysis

Statistical analysis of correlation of the tumour size by each of the imaging modalities with the size on histological examination was performed by calculating Pearson's correlation coefficient using the statistical software Statistical Package for the Social Sciences for Windows™ version 9 (SPSS®, Chicago, Illinois, USA).

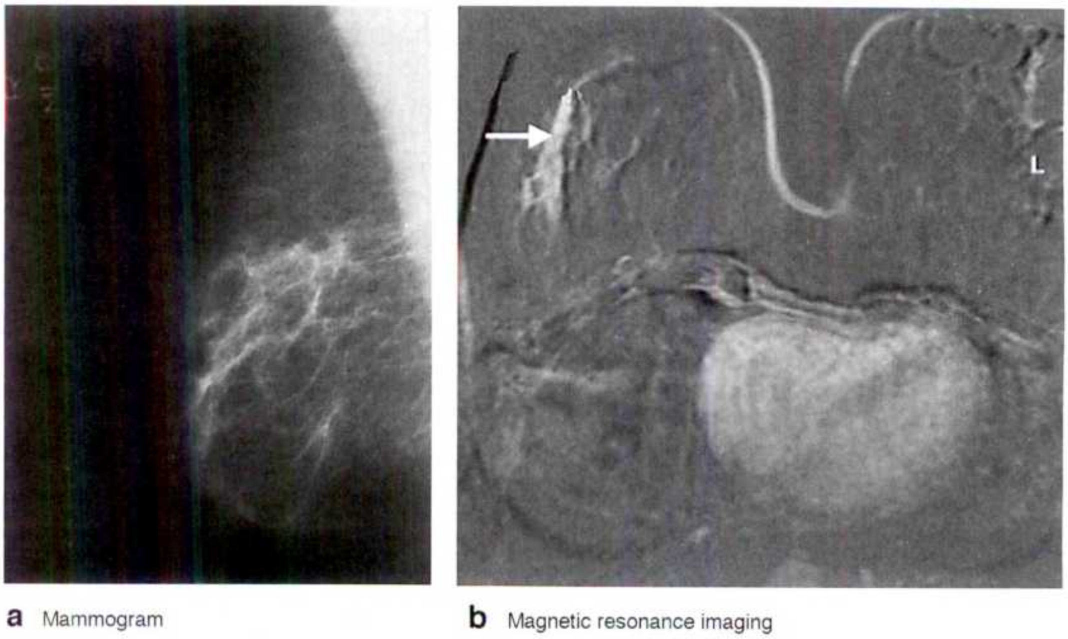
Results

Magnetic resonance imaging as an aid to diagnosis

MRI accurately identified cancer in four patients in whom both mammography and ultrasonography were normal. Two of these patients had presented with distortion of the breast contour without a palpable abnormality (*Fig. 1*), while two presented with a distortion of the breast with an underlying soft, indistinct lump. MRI also accurately identified cancer in the fifth patient, who presented with metastatic axillary adenocarcinoma and presumed occult primary tumour in the breast. Clinical examination of the breasts as well as both mammography and ultrasonography were normal (*Fig. 2*).

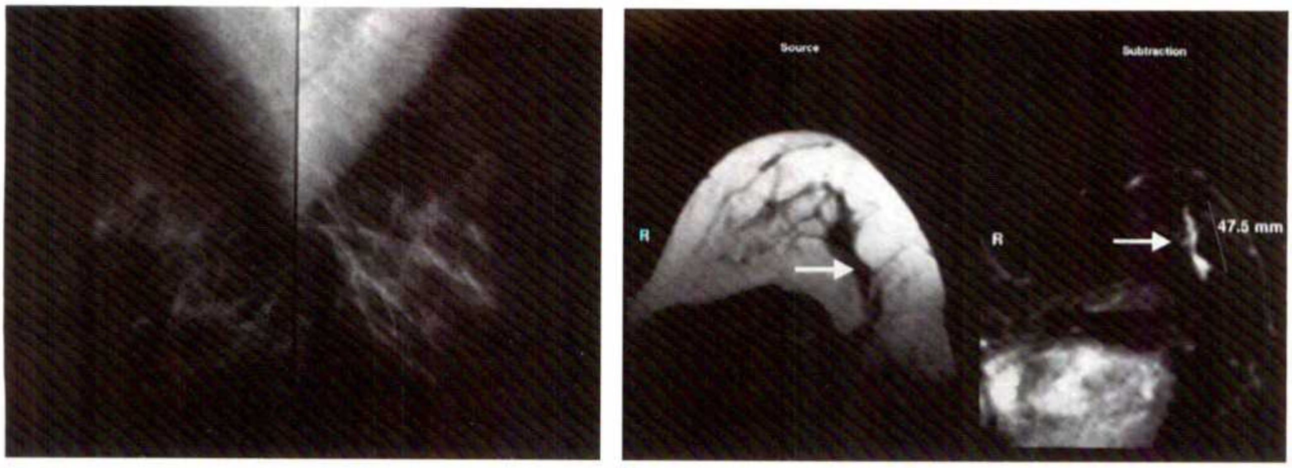
In all patients in whom MRI alone identified tumour, the lesion was subsequently identified on directed ultrasonography as a mild disruption of the normal echotexture of the breast. A preoperative diagnosis of malignancy using ultrasonographically guided FNAC or core biopsy was achieved in all patients.

MRI failed to identify tumour in one patient, aged 61 years, who presented with an area of soft nodularity within the breast that was clinically categorized as indeterminate. Mammography, ultrasonography and FNAC, performed twice, showed no evidence of malignancy. MRI showed increased uptake of contrast, but the enhancement profile was not characteristic of malignancy and was reported as indeterminate (R3). A subsequent core biopsy showed ILC and mastectomy revealed a 40-mm ILC. The sensitivity of mammography, ultrasonography, FNAC and MRI for the detection of ILC in this subgroup of 20 patients is shown in *Table 1*.



a Mammogram **b** Magnetic resonance imaging

Fig. 1 **a** Normal right mammogram. **b** Dynamic contrast-enhanced magnetic resonance imaging showed a suspicious enhancing lesion (arrow) in the right breast. Subsequent histological examination showed invasive lobular carcinoma



a Mammogram

b Magnetic resonance imaging

Fig. 2 **a** Bilateral mammograms in a patient with a lymph node in the left axilla containing metastatic adenocarcimona did not show any abnormality. **b** Precontrast and postcontrast magnetic resonance imaging showing an enhancing lesion (arrows) suggestive of a primary tumour in the left breast

Table 1 Sensitivity of mammography, ultrasonography, fine-needle aspiration cytology and magnetic resonance imaging for diagnosis of invasive lobular carcinoma

Investigation	No. of true positives	Sensitivity (%)
Mammography (*n* = 20)	10	50
Ultrasonography (*n* = 20)	14	70
FNAC (*n* = 16)	12	75
MRI (*n* = 20)	19	95

FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging

Tumour extent

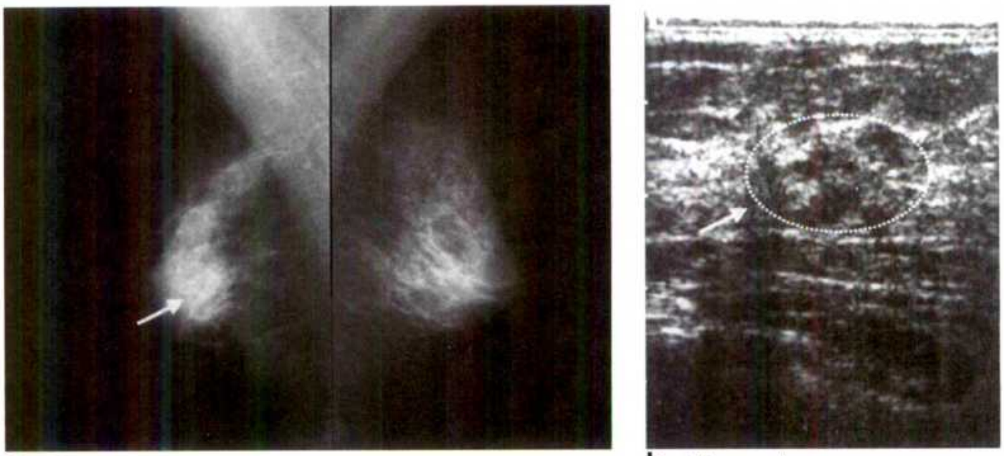
Nine of 14 patients with ILC in whom MRI was performed to determine tumour extent underwent a mastectomy while five were treated with breast-conserving surgery. The margins of excision were clear of tumour in all patients treated with breast-conserving surgery.

The pathological maximum diameter of the tumours ranged from 8 to 130 mm and correlated better with MRI size ($r = 0{\cdot}967$) than size estimated by mammography ($r = 0{\cdot}663$) and ultrasonography ($r = 0{\cdot}673$). This correlation enabled single-stage surgical resection in all patients. In seven of 14 patients in whom MRI was performed to determine tumour extent, MRI gave significant additional information about tumour extent that had an impact on surgical treatment. In four patients conventional imaging grossly underestimated the size of the tumour compared with that on subsequent histological examination (size on histology was more than twice the predicted size on mammography and ultrasonography), while a good correlation was seen between the size of the tumour on MRI and histology (*Fig. 3*). As MRI showed tumour size greater than 40 mm, a mastectomy was performed in these patients. Had MRI not been performed, three of these patients would have fulfilled the conventional criteria for breast-conserving surgery, but ultimately would have required a completion mastectomy because of the extensive nature of the malignancy.

MRI accurately predicted infiltration of the underlying pectoral muscle in one patient that was not apparent on clinical examination or conventional imaging. In two patients with a suspected multicentric tumour in one breast, MRI identified a tumour in the contralateral breast. MRI did not overestimate tumour size or identify false-positive foci of malignancy in any patient. No patient underwent an unnecessary mastectomy based on MRI.

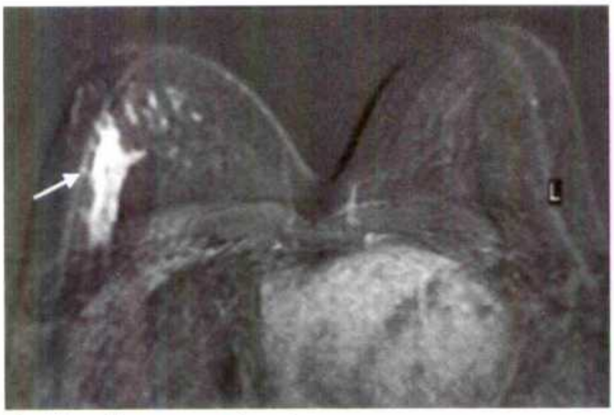
Discussion

ILCs often present with subtle clinical signs[2,3] and minimal mammographic abnormality[4,5]. The present results have shown that MRI has a higher sensitivity than mammography and ultrasonography in the diagnosis of ILC. Distortion of the breast is an important clinical sign and can be a marker of underlying malignancy, even in the absence of a definite palpable abnormality and the finding of normal imaging. MRI should therefore be performed in patients with normal mammography and ultrasonography if there is a clinical suspicion of malignancy. MRI is also extremely useful in identifying tumour within the breast in



a Mammogram

b Ultrasound



c Magnetic resonance imaging

Fig. 3 **a** Mammography showed an area of parenchymal distortion in the right breast (arrow). **b** Ultrasonography showed an area of disruption of the normal echotexture measuring 15 mm (circle). **c** Dynamic contrast-enhanced magnetic resonance imaging showed a large 70-mm enhancing lesion in the right breast (arrow). Subsequent mastectomy revealed a 60-mm invasive lobular carcinoma

patients who present with metastatic axillary lymph nodes and a presumed occult primary breast tumour.

The specificity of breast MRI in previous studies has been variable, ranging from 37 to 97 per cent[22]. In this study there were no false-positive MRI scans. A limitation of MRI is the low availability of an MRI-guided breast biopsy system. However, this can be overcome by the use of targeted ultrasonography and ultrasonographically guided FNAC or core biopsy directed by the information obtained on MRI.

This and previous studies have shown that both mammography[8–10] and ultrasonography[10] can greatly underestimate the size of an ILC. Tumour-free resection margins are critical to obtain acceptably low local recurrence rates if breast-conserving surgery is performed[23–26]. However, several studies have highlighted the difficulty in obtaining tumour-free margins at initial operation in patients with ILC compared with IDC[8,9,11,12]. Up to 63 per cent of patients with ILC have margins involved with tumour when breast-conserving surgery is attempted[12]. In this context, MRI is particularly valuable in accurately delineating the extent of the cancer, thereby identifying those patients unsuitable for breast-conserving surgery. MRI also minimizes the chance of involvement of the surgical margins in patients in whom breast-conservation surgery is feasible. By accurately assessing the size of primary tumours MRI provides valuable information for preoperative planning and single-stage resection of ILC, which has obvious advantages in terms of cost, resources and avoiding extra physical and psychological morbidity for patients.

Limitations of cost and availability preclude the widespread use of MRI in the evaluation of all patients presenting with breast disease or indeed all patients with breast cancer. However, in view of its particular advantages in the diagnosis and preoperative characterization of ILC, the authors recommend its use in patients with known or suspected ILC.

Acknowledgements

K. Munot is a Clinical Research Fellow funded in part by the Breast Cancer Research Action Group.

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Original article

Enhanced antitumour efficacy by combining conventional chemotherapy with angiostatin or endostatin in a liver metastasis model

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Background: Tumour-induced microvascular networks have become attractive targets in cancer therapy. Strategies that target both tumour cells and vasculature have not been investigated in models of early metastatic colorectal disease. The efficacy of a combination of conventional chemotherapy with a potent angiogenesis inhibitor (endostatin or angiostatin) in a murine model of early colorectal liver metastasis was studied.

Methods: Sixty-six mice were subjected to intrasplenic injection of C26 tumour cells to induce colorectal liver metastases. Control animals received phosphate-buffered saline ($n = 8$) or citrate buffer ($n = 8$). Treatment included conventional chemotherapy ($n = 9$), endostatin ($n = 8$), high-dose ($n = 5$) or low-dose (one-tenth of optimal dose; $n = 10$) angiostatin, as well as the combination of either of these drugs with chemotherapy ($n > 5$). Clinical appearance was scored daily using a semiquantitative scale. Liver weight, macroscopic and histological tumour involvement (hepatic replacement area; HRA) were measured upon death at day 12.

Results: Treated mice displayed significantly better clinical scores than controls, except for those animals treated with low-dose angiostatin with or without chemotherapy. Treatment with conventional chemotherapy resulted in a decrease in HRA from 42·3 to 29·1 per cent ($P < 0{\cdot}001$). The addition of angiostatin or endostatin to conventional chemotherapy improved antitumoral efficacy, in a multiplicative manner, resulting in a HRA of approximately 3·5 per cent ($P < 0{\cdot}001$).

Conclusion: The addition of angiostatin or endostatin to conventional chemotherapy enhanced antitumoral efficacy in a murine model of early colorectal liver metastasis.

Paper accepted 29 April 2002

British Journal of Surgery 2002, **89**, 1302–1309

Introduction

Colorectal cancer is one the most prevalent malignancies in developed countries[1]. Secondary malignant hepatic disease will develop in as many as 50–80 per cent of these patients[2], and is the sole site of initial recurrence in approximately 30 per cent[3]. Once colorectal liver metastases have developed, the natural course of the disease is associated with a poor survival rate[4]. Partial liver resection offers the only hope of cure for these patients[5], but is, unfortunately, restricted to selected patients, many of whom will still have recurrence within the liver or develop extrahepatic metastases.

As a result of the use of adjuvant chemotherapy, survival rates of patients with colorectal carcinoma have improved. As a consequence, adjuvant chemotherapy has become standard practice in high-risk patients after operation. Studies of chemotherapy before or after liver resection for secondary malignant disease, however, have been contradictory[6–8], although responses to schemes including oxaliplatin have recently been shown to increase the resectability rate of liver metastases[7]. These results indicate that there is room for improvement, particularly regarding perioperative systemic treatment. A search for alternative treatment modalities for colorectal liver metastases is therefore warranted.

One promising antitumour strategy involves antiangiogenic treatment. This approach aims to suppress metastatic outgrowth by inhibiting the formation of a tumour-induced vascular network. Many antiangiogenic agents are being tested in preclinical and clinical trials[9]. Experimental models have shown that when tumours are deprived of new blood vessels they remain in a microscopic state of dormancy[10]. As antiangiogenic drugs are directed against components of developing vasculature, they may be expected to lead to stable disease, rather than complete remission, and may have little or no effect on gross or bulky (metastatic) disease. Moreover, discontinuation of antiangiogenic therapy may allow the tumour or its metastases to resume growth[10–12]. Hence, patients most suitable for long-term antiangiogenic treatment may be those with 'early metastatic' or 'minimal residual' disease.

Combining conventional chemotherapy with antiangiogenic compounds might lead to improved antitumour efficacy by targeting both tumour cell and endothelial cell compartments[13–18]. Strategies combining these two targets have not, however, been investigated thoroughly in models of early widespread metastatic colorectal liver disease[19–24].

In this study, the efficacy of combinations of conventional chemotherapy and strong angiogenesis inhibitors was assessed in a murine model of early metastatic colorectal cancer. The effects of the combination therapies were compared with those of conventional and antiangiogenic agents alone.

Materials and methods

Drugs

Angiostatin

Human angiostatin was purified as described by O'Reilly *et al.*[25], with minor modifications[12]. Outdated human plasma was applied to a lysine-Sepharose column (Pharmacia, Uppsala, Sweden). Plasminogen was eluted with ε-aminocaproic acid 0·2 mol/l and dialysed against distilled water (molecular weight cut-off: 6–8000 Spectra/Por (Spectrum Laboratories, Rancho Dominguez, California, USA); dilution greater than 4×10^7; 4°C), buffered with Tris 7·6 20 mmol/l, followed by proteolytic digestion with plasminogen porcine pancreatic elastase (Calbiochem, San Diego, California, USA) 0·8 units/mg (shaken overnight at 37°C; 120 r.p.m.). The solution was applied to the same column and eluted with ε-aminocaproic acid 0·2 mol/l, while the flow-through was collected and treated as recently cleaved plasminogen, in order to collect angiostatin fragments with low lysine affinity. The angiostatin was dialysed and freeze-dried. The angiostatin and its flow-through were subsequently combined. The bioactivity of the angiostatin was confirmed by means of the mouse cornea neovascularization assay, as described elsewhere[12].

In all experiments the administration of angiostatin was as follows. Mice were given a dorsal osmotic pump (Alzet™ pump, type 2001; Alza, Palo Alto, California, USA) subcutaneously for continuous administration of angiostatin in a dose of 100 mg/kg daily. In previous work this dose was shown to elicit maximal antitumour effects[12]. This concentration is subsequently referred to as 'high dose'. In addition, one-tenth of this dose (10 mg/kg daily) was used to study any additional effect over conventional chemotherapy of low amounts of angiostatin.

Endostatin

Human recombinant endostatin™ produced in *Pichia pastoris* (Entremed, Rockville, Maryland, USA) was administered by daily subcutaneous injection of 100 µl in a dose of 500 µg/day. Control animals received the solvent citrate buffer (17 mmol/l citric acid, 59 mmol/l sodium chloride, 66 mmol/l sodium phosphate, pH 6·2) 100 µl/day subcutaneously.

Chemotherapy

Doxorubicin® (Pharmacia and Upjohn, Woerden, The Netherlands), in a dose of 10 mg/kg body-weight, was administered intravenously by tail vein injection once on postoperative day 3[26]. Controls received an equal volume of PBS intravenously.

Tumour cell line

The murine colonic carcinoma cell line C26 was cultured in Dulbecco's modified Eagle's medium supplemented with 10 per cent heat-inactivated fetal calf serum, penicillin 100 units/ml and streptomycin 100 µg/ml in a 10 per cent carbon dioxide environment. Cell viability was determined by trypan blue staining.

Confluent cultures were harvested by brief trypsinization (0·05 trypsin in 0·02 per cent ethylenediamine tetra-acetic acid), to a final concentration of 1×10^5 cells per 100 µl PBS.

Animals

The animals studied were male Balb/c mice, aged 10 weeks, purchased from the General Animal Laboratory of the University Medical Centre Utrecht. They were housed under standard conditions and allowed food and water *ad libitum*. All experiments were carried out according to the guidelines of the Animal Welfare Committee of the University Medical Centre Utrecht.

Mice were anaesthetized intraperitoneally with fentanyl citrate–fluanisone (0·3 mg per mouse; Janssen-Cilag, Brussels, Belgium) and midazolam chloride (12·5 mg per mouse; Roche, Brussels, Belgium). The spleen was exteriorized through a left lateral flank incision. Some 1×10^5 C26 colorectal carcinoma cells per 100 μl were injected into the spleen parenchyma using a 27-G needle. After 10 min, the spleen was removed to prevent intrasplenic tumour growth. The peritoneum and skin were closed in two layers with 5/0 polyglactin.

Study design

Mice were subsequently divided into the following groups: controls received PBS ($n = 8$) or citrate buffer ($n = 8$). Conventional chemotherapy alone consisted of doxorubicin ($n = 9$). Single-agent antiangiogenic therapy included high-dose angiostatin ($n = 5$), low-dose angiostatin ($n = 10$) or endostatin ($n = 8$). Combination therapies included treatment with high- or low-dose angiostatin combined with doxorubicin ($n = 4$ and $n = 9$ respectively) or endostatin combined with doxorubicin ($n = 5$). The treatment was initiated 6 h after tumour cell injection based on calculations for tumour cell arrest and extravasation[27].

The clinical appearance of the mice was scored daily by two independent observers blinded to the treatment, according to the scoring system provided by the animal facility (*Table 1*).

All mice were killed on day 12 after tumour implantation. Livers were collected for the analysis of wet liver weight and hepatic replacement areas (HRAs).

Table 1 Clinical appearance scoring system

	Score
Appearance	
Normal	0
Fur untreated	1
As above + red spots around eyes	2
As above + abnormal posture	3
Behaviour	
Normal	0
Minor changes	1
Decreased activity	2
Immobility	3
Reactivity	
Normal	0
Increased or reduced	1
As above but more so	2
As above but even more so	3
Body-weight	
Normal	0
Approx. 10 per cent weight loss	1
Approx. 20 per cent weight loss	2
More than 20 per cent weight loss	3

Histological analysis

Formalin-fixed livers were sectioned into 4-mm slices and embedded completely in paraffin. For each liver, four non-sequential 4-μm slides were stained with haematoxylin and eosin, and analysed. The HRA was defined as the percentage of normal hepatic tissue that had been taken up by metastatic tumour cells, and assessed morphometrically in a semiquantitative manner (Leica-Q-Prodit, Leica Microsystems, Ryswyk, The Netherlands). A four-grid analysis was used to determine the area ratio in 100 fields per slide. According to this protocol, a 5 per cent confidence interval can be achieved[28].

Statistical analysis

For differences in clinical scores, the *post hoc* test of repeated measurements analysis of variance (ANOVA) was performed. The independent t test was used to compare the various treatment groups. The interaction effects between the different antiangiogenic drugs in combination with conventional chemotherapy were tested with ANOVA. A multiplicative effect was defined as an enhanced effect of antiangiogenic therapy in the presence of chemotherapy, or *vice versa*. Intrahepatic tumour load (HRA) was expressed as a percentage of the total liver area. Relative HRA was defined as the HRA resulting from a particular treatment modality in relation to the HRA following conventional chemotherapy alone (100 per cent).

Results are presented as mean(s.e.m.). Differences were considered significant when $P < 0.003$ for t test calculations (Bonferroni correction for high number of tests) and when $P < 0.05$ for ANOVA.

Results

Clinical appearance

Mice treated with either drug displayed a significantly better clinical score than the (citrate) control animals, except for those treated with low-dose angiostatin or its combination with chemotherapy. The clinical appearance scores showed an increase on days 3–5 for all mice treated with chemotherapy, indicating a transient adverse effect on clinical condition on the days immediately after intravenous injection (*Fig. 1*).

Macroscopic appearance and liver weight

The macroscopic appearance of tumour-bearing control livers was distinctive from that of treated livers (*Fig. 2*). Livers of untreated animals were enlarged, showing an

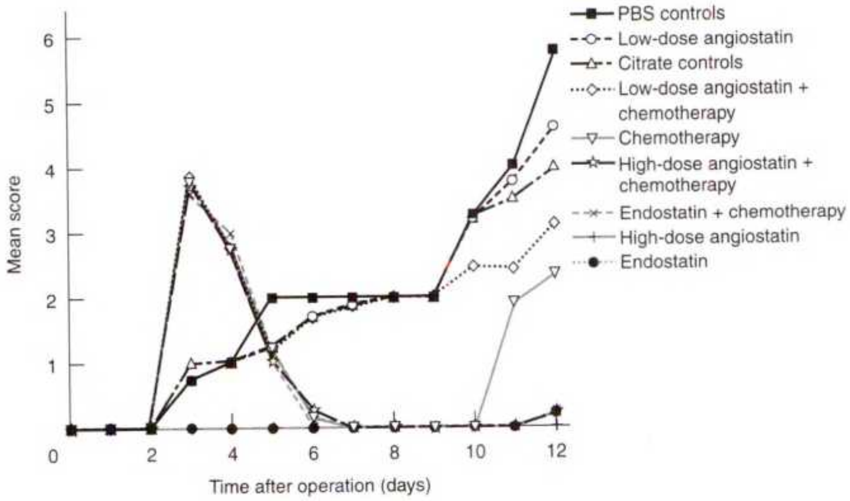
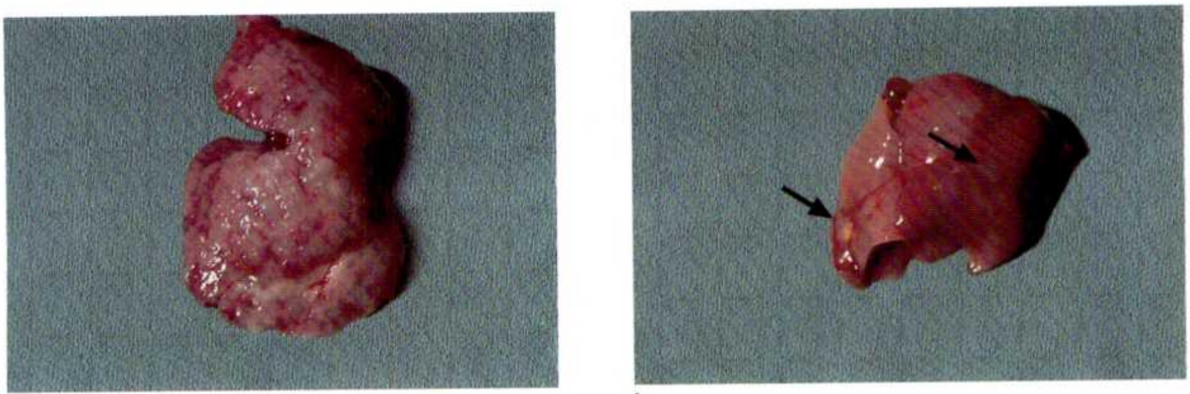
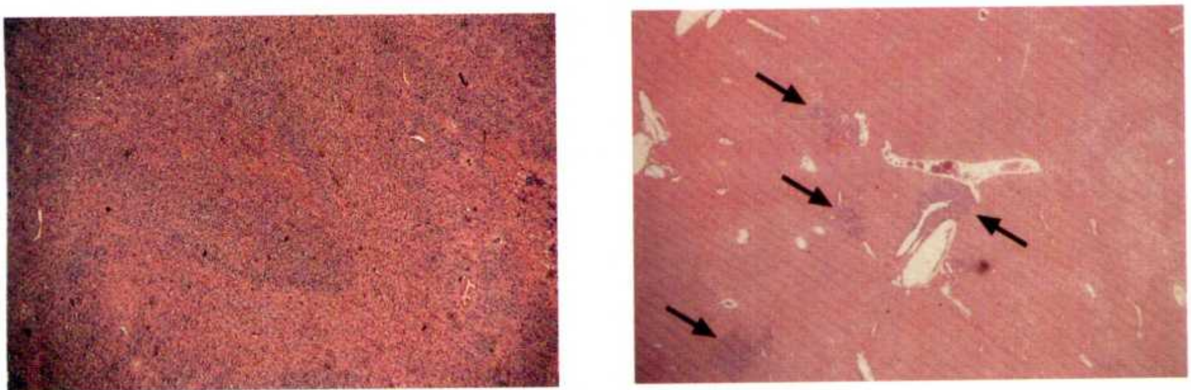


Fig. 1 Course of clinical appearance from the day of operation (day 0) until the day of death (day 12). The appearance of each mouse was scored by two independent observers in a semiquantitative manner. The scoring system used is depicted in *Table 1*; note that the lower the score, the healthier the animal (a normal mouse has a cumulative score of 0). Scores are plotted per treatment group; mean values are given. PBS, phosphate-buffered saline



a Untreated control

b Endostatin and chemotherapy



c Untreated control

d Endostatin and chemotherapy

Fig. 2 The macroscopic and histological (stained with haematoxylin and eosin) appearance of resected livers. **a** The irregular white surface is due to excessive tumour growth. **b** This is significantly reduced by endostatin and chemotherapy. **c** Normal liver architecture is highly disturbed by tumour (hepatic replacement area (HRA) 53 per cent). **d** After combination treatment infiltration by tumour is significantly less (HRA 5 per cent). Arrows indicate metastatic lesions

irregular liver surface caused by extensive tumour growth, whereas those of treated animals were smaller in size, having a macroscopically normal appearance with smoother, elastic, normal texture. The mean(s.e.m.) liver weight of mice treated with endostatin (1·4(0·1) g) or with endostatin in combination with chemotherapy (1·2(0·1) g) was significantly decreased compared with that in untreated tumour-bearing livers (2·5(0·2) g) ($P = 0.002$ and $P < 0.001$ respectively.) Non-tumour-bearing control age-matched mice had a mean liver weight of 1·2(0·1) g (data not shown).

Antitumour effect

Table 2 and *Fig. 3* summarize the results of the histological analysis of the HRAs in the various groups. Respective *P* values for comparisons between individual treatment groups are outlined in *Table 3*. All single-agent drugs gave superior results with regard to antitumour efficacy compared with no treatment ($P < 0.001$).

Table 2 Tumour hepatic replacement area per treatment group on day 12 after C26 intrasplenic tumour injection to induce liver metastases

	Hepatic replacement area (%)	
	No chemotherapy	Chemotherapy
Controls	42·3(2·0)	29·1(0·9)
High-dose angiostatin	8·6 (2·6)	3·3(1·4)
Low-dose angiostatin	27·2(1·0)	8·7(0·7)
Endostatin	12·4(1·4)	3·8(1·1)
Citrate	42·1(5·9)	

Values are mean(s.e.m.). Statistical differences are shown in *Table 3*

Chemotherapy monotreatment

In a pilot experiment, the optimal antitumour dose (HRA 25–30 per cent) resulted in a high clinical score (greater than 6), indicating a toxic response to chemotherapy (data not shown). A suboptimal antitumour dose, resulting in a significant antitumour effect but with diminished, moderate toxicity, was determined, as judged by a clinical score below 4 (*Fig. 1*). All experiments were carried out with this suboptimal reduced-toxicity dose of chemotherapy. The treatment of liver metastases with this dose of doxorubicin monotherapy ($n = 5$) resulted in a decrease in mean(s.e.m.) HRA, from 42·3(2·0) (95 per cent confidence interval (c.i.) 37·5 to 47·0) per cent in non-treated controls to 29·1(0·9) (95 per cent c.i. 27·2 to 31·1) per cent ($P < 0.001$) (*Tables 2* and *3*; *Fig. 3*).

Angiostatin

As shown in *Tables 2* and *3*, and in *Fig. 3*, high-dose treatment ($n = 5$) resulted in a mean(s.e.m.) HRA of 8·6(2·6) (95 per cent c.i. 1·4 to 15·8) per cent ($P < 0.001$). Low-dose angiostatin ($n = 10$) resulted in a HRA of 27·2(1·0) (95 per cent c.i. 25·0 to 29·4) per cent ($P < 0.001$). The addition of high- and low-dose angiostatin to the conventional chemotherapy improved antitumour efficacy, resulting in HRAs of 3·3(1·4) (95 per cent c.i. – 1·1 to 7·6) and 8·7(0·7) (95 per cent c.i. 7·1 to 10·2) per cent respectively. High-dose

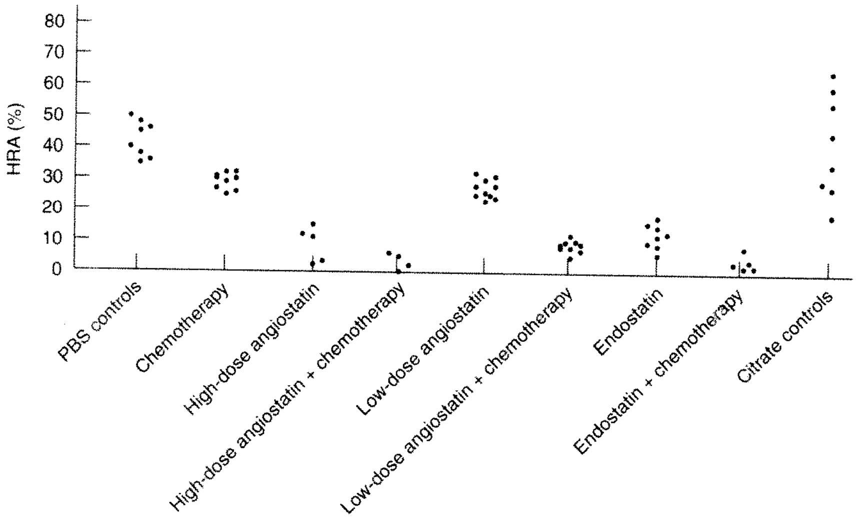


Fig. 3 Results of tumour hepatic replacement area (HRA) in each treatment group on day 12 after C26 intrasplenic tumour injection to induce liver metastases. PBS, phosphate-buffered saline

angiostatin added to conventional chemotherapy was not significantly more effective than high-dose angiostatin monotherapy ($P = 0\cdot135$). However, low-dose angiostatin combined with conventional chemotherapy significantly enhanced antitumour efficacy when compared with low-dose angiostatin alone ($P < 0\cdot001$).

When compared with chemotherapy alone, the effect of addition of angiostatin to chemotherapy was multiplicative for both high-dose ($P = 0\cdot047$) and low-dose ($P = 0\cdot029$) angiostatin, as shown in *Fig. 4*. The effect of the addition of low-dose angiostatin to chemotherapy on the relative HRA was also multiplicative ($P < 0\cdot001$).

Endostatin

Endostatin monotherapy resulted in a mean(s.e.m.) HRA of 12·4(1·4) (95 per cent c.i. 9·1 to 15·7) per cent) ($P < 0\cdot001$) (*Tables 2* and *3*; *Fig. 3*). Addition to the conventional chemotherapy regimen further reduced the hepatic tumour load to a HRA of 3·8(1·1) (95 per cent c.i. 0·7 to 6·9) per cent ($P < 0\cdot001$). Again, co-administration of the antiangiogenic agent and conventional chemotherapy was multiplicative with regard to the effect on the relative HRA ($P = 0\cdot017$).

Discussion

In this murine model of early colorectal liver metastases, the addition of angiostatin or endostatin to a conventional chemotherapeutic agent improved antitumour efficacy compared to chemotherapy alone. These results support the concept that combined cytotoxic and antiangiogenic therapy may improve results in the treatment of microscopic colorectal liver metastases.

Table 3 Statistical analysis of hepatic replacement area per treatment group on day 12 after C26 intrasplenic tumour injection to induce liver metastases

Agents	*P**
Controls *versus* all agents	< 0·001
Citrate *versus* endostatin	0·001
Citrate *versus* endostatin + chemotherapy	< 0·001
Chemotherapy *versus* high-dose angiostatin + chemotherapy	< 0·001
Chemotherapy *versus* low-dose angiostatin + chemotherapy	< 0·001
Chemotherapy *versus* endostatin + chemotherapy	< 0·001
High-dose angiostatin *versus* high-dose angiostatin + chemotherapy	0·135
Low-dose angiostatin *versus* low-dose angiostatin + chemotherapy	< 0·001
Endostatin *versus* endostatin + chemotherapy	0·001

*Independent *t* test with Bonferroni correction

Compared with monotherapy chemotherapeutic regimens, the antitumour effect of combined chemotherapeutic and antiangiogenic agents was multiplicative (*Fig. 4*); the combination was more effective than the sum of effects of either monotherapies, suggesting synergy between the agents. Thus, the rationale of the combination strategy, i.e. targeting two separate cell populations (tumour cells and endothelial cells), is supported by this study. In apparent contrast to these findings, some authors have speculated that treatment targeting the vasculature (vascular endothelial growth factor) could hamper other blood-borne therapeutic agents from reaching tumour cells[29,30]. A combination of tumour necrosis factor α and melphalan, however, was shown to generate a higher intratumoral concentration of the cytotoxic agent than chemotherapy alone[31]. Recently, Jain[32] suggested that antiangiogenic therapy may lead to 'normalization' of tumour vasculature before its destruction. The effect of chemotherapy during the normalization phase might be enhanced, rather than being inhibited at a later stage once vasculature has been destroyed.

Another advantage of combination strategies might be a dose reduction of the individual drugs involved, without impairing antitumour efficacy. Based on experimental data, antiangiogenic agents are believed generally to be safe,

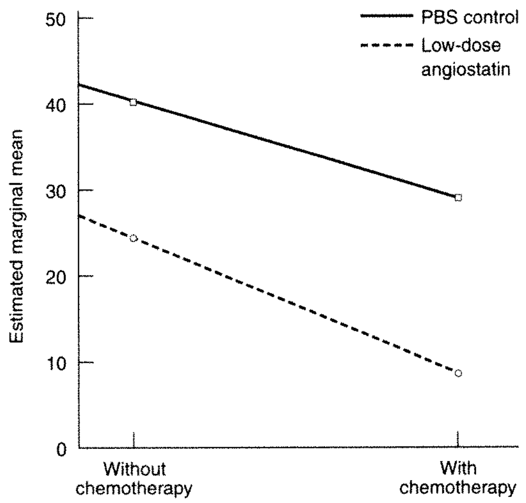


Fig. 4 Results of the univariate analysis of variance to calculate the interaction effect of low-dose angiostatin (10 mg per kg per day, continuously) in combination with conventional chemotherapy (doxorubicin). The solid line represents the effect of chemotherapy alone on the hepatic tumour load (hepatic replacement area; HRA) and the dashed line shows the effect of low-dose angiostatin in combination with chemotherapy on the HRA. The multiplicative effect of the combination was significant ($P = 0\cdot029$, univariate analysis of variance)

although some caution should be exercised, because the authors' group recently showed that angiostatin, administered in a high dose immediately after primary colonic anastomosis, results in impaired healing[33]. In the present experimental study, treatment with low-dose angiostatin combined with relatively low doses of conventional chemotherapy was effective, and the mice displayed only minor toxicity throughout the treatment period. Antiangiogenic scheduling of treatment by lowering the dose with increased frequency of administration, has also proved effective[34].

This study employed an experimental model that resembles the most suitable patient category ('early' metastatic disease). This is important because most angiogenesis inhibitors that are currently in clinical trials are being administered to patients with bulky end-stage tumours. This is also true for the combination strategies currently under study[35]. Only a few trials are evaluating the efficacy of the combination of antiangiogenic and chemotherapeutic agents in an adjuvant setting[15,35]. Based on the action of antiangiogenic therapy, i.e. preventing outgrowth of microscopic tumour deposits, few or no antitumour effects may be anticipated in bulky disease, and the selection of suitable patient categories is required before efficacy can be established. Although doxorubicin is not used conventionally in the treatment of human colorectal cancer, there is a large body of literature confirming the biological relevance of this murine model for colorectal metastatic disease[26,36]. The results of the present study on experimental early colorectal liver metastases indicate that antiangiogenic therapy may be highly attractive for perioperative treatment schedules.

Future clinical studies evaluating the effectiveness of combination strategies should be undertaken in a perioperative setting so that assessment can be made of antiangiogenic agents in multidrug therapy of patients with 'early' metastatic or 'minimal residual' disease.

Acknowledgements

The authors are grateful for the statistical support offered by E. P. Martens, Department of Biostatistics, University of Utrecht, and thank A. Reijerkerk, Laboratory of Medical Oncology, University Medical Centre Utrecht, for his expert contribution to cell culture maintenance, and A. Verheem, technician, for surgical assistance. This work was supported by the Netherlands Organization for Scientific Research (NWO) – Medical Sciences (project no. 99 054).

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Original article

Outcome of patients with severe chronic pain following repair of groin hernia

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Background: Chronic pain is the most serious long-term complication that can occur after repair of a groin hernia. The aim of this study was to assess the outcome of patients who report severe or very severe pain 3 months after groin hernia repair.

Methods: This was a population-based study of all patients who underwent repair of a groin hernia between April 1998 and March 1999 in Scotland. All received a postal questionnaire 3 months after hernia repair and those who reported severe or very severe pain at the operation site were asked to complete a further questionnaire 2·5 years later. The main outcome measure included the number of patients with persistent pain and the effect of pain on daily activities and quality of life.

Results: Of 5506 patients who underwent repair of a groin hernia, 4062 (74 per cent) returned the first questionnaire and 125 (3 per cent) reported severe or very severe pain. Eight-six (72 per cent) of 120 patients (five had died or could not be contacted at the original address) replied to the second questionnaire; 61 (71 per cent) still reported pain, which was severe or very severe pain in 22 (26 per cent) and mild or very mild in 39 (45 per cent). Twenty-nine (48 per cent) sought further medical help from their general practitioner or surgeon. Nine (15 per cent) attended a pain clinic while five (8 per cent) had further surgery. Chronic pain had significant effects ($P < 0{\cdot}001$) on all daily activities including walking, work, sleep, relationships with other people, mood and general enjoyment of life.

Conclusion: Chronic pain persists in most patients who report severe or very severe pain at 3 months after hernia repair, and has a significant effect on the patients' daily activities and quality of life.

Paper accepted 5 June 2002

British Journal of Surgery 2002, **89**, 1310–1314

Introduction

Severe chronic pain is the most serious long-term complication that can occur after repair of a groin hernia. In the past this has been thought to be a rare complication[1] but more recently prospective and population-based studies have indicated that up to 6 per cent of patients may have moderate to severe pain 1 year after this operation[2,3]. In all over a third of patients will report some form of pain at 1 year after operation[2–5].

Given that groin hernia repair is a common operation with an annual rate of repair of around 100–150 per 100 000 of the population[6], in a country the size of the UK over 5000 new patients may suffer moderate to severe chronic groin pain each year. This has obvious cost implications for the health service as well as the economy as a whole. Many of these patients will have a significant delay in return to work and normal activities, and some may not be able to resume their normal employment[7]. This paper reports the outcome of patients who had severe or very severe pain 3 months after groin hernia repair in Scotland. This is the period beyond which normal tissue healing is assumed to have occurred and fulfils the International Association for the Study of Pain definition of chronic pain[8].

Patients and methods

Between April 1998 and March 1999 data were gathered on patients who underwent repair of a groin hernia in Scotland[9]. At a minimum of 3 months after operation all were sent a modified Short Form (SF) 36[5,9], with a reminder if there was no reply, to assess their outcome and satisfaction with the operation. All were asked whether they had suffered pain in the groin at the site of hernia repair in the past week. In addition all male patients were asked if they had pain in the testis on the same side. Those that had pain were asked to grade it as very mild, mild, severe or very severe. Patients were also asked about numbness around the groin and in the thigh on the side of the hernia operation.

Patients who reported severe or very severe pain were sent a further questionnaire in April 2001. In addition to the modified SF-36 they were asked about the character of the pain and received a Wisconsin Brief Pain Questionnaire[10]. The latter is designed to assess the effect of pain on general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. Patients score from 0 (if pain does not interfere) to a maximum of 10 (if it completely interferes with any of the above activities). The words used to describe the character of the patients' pain were based on previous studies[11,12] that set out to validate verbal responses for neuropathic (pain related to nerve injury) or nociceptive (pain related to tissue injury) pain. Patients were also asked whether they suffered from other chronic pain conditions such as chronic backache, headache, irritable bowel syndrome or any other chronic condition associated with pain.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences for Windows™, version 9.01 (SPSS®, Chicago, Illinois, USA). χ^2 or Fisher's exact test was used to examine any association between variables and whether the pain was very mild–mild or severe–very severe. A *t* test was used to examine the effect of chronic pain on daily activities and quality of life. Data are presented where appropriate with 95 per cent confidence intervals.

Results

Details were obtained on 5506 patients who had a groin hernia repair in Scotland in 1998, of whom 4062 (74 per cent) returned the modified SF-36 questionnaire. Some 1733 (43 per cent) still had very mild or mild pain while 125 (3 per cent) had severe or very severe pain at the site of the hernia repair. Patients with severe or very severe pain were significantly younger (54 *versus* 60 years; $P < 0{\cdot}001$) and more likely to be female (odds ratio 1·73 (95 per cent confidence interval 1·07 to 2·81)) compared with the total population that had a hernia. There was no association between severe or very severe pain following operation and hernia type (primary or recurrent), operation type (mesh or non-mesh), grade of operator and whether the operation was performed as a day case or not.

In April 2001, a median of 30 months after groin hernia repair, 86 (72 per cent) of the 120 patients (five had died or could not be contacted at the original address) with severe or very severe pain replied to the second questionnaire (*Table 1*). Twenty-five (29 per cent) recorded no pain at the site of the hernia while 39 (45 per cent) described the pain as very mild or mild. Twenty-two (26 per cent) still had severe or very severe pain. Of the 61 patients with pain, 39 (64 per cent) had groin pain, one (2 per cent) had testicular pain and 21 (34 per cent) had both groin and testicular pain. Seventeen patients (28 per cent) described the pain as continuous while 36 (59 per cent) felt that it was brought on by activity. Twenty-six (43 per cent) had been back to the general practitioner with pain and 18 (30 per cent) had returned to the surgeon. Five (8 per cent) had further surgery and nine (15 per cent) had attended a pain clinic. Patients with severe or very severe pain were significantly more likely to have sought further treatment than those with very mild or mild pain (19 of 22 *versus* ten of 39; $P < 0{\cdot}001$).

Table 1 Demographic details of 86 patients who completed the second questionnaire

Age*	54 (40–66)
Sex ratio (M : F)	74 : 12
Hernia type	
Primary	73 (85)
Recurrent	13 (15)
Bilateral	7 (8)
Inguinal	83 (97)
Femoral	3 (3)
Operation type	
Open mesh	77 (90)
Open non-mesh	8 (9)
Laparoscopic	1 (1)
Principal surgeon	
Senior house officer	16 (19)
Registrar	27 (31)
Staff grade	8 (9)
Associate specialist	2 (2)
Consultant	33 (38)

*Values are median (interquartile range); other values in parentheses are percentages

Effects on daily activities and quality of life

The presence of chronic pain interfered significantly ($P < 0{\cdot}001$) with all of the activities measured irrespective of whether the pain was very mild, mild, severe or very severe. Not surprisingly this effect was more marked in the severe–very severe group. (*Table 2*).

Character of pain and numbness

The most common descriptor of pain used in this study was aching (45 per cent), followed by throbbing (28 per cent) and stabbing (23 per cent). Patients with very mild or mild pain were more likely to describe the pain using a single term that indicated that the character of the pain was either neuropathic or nociceptive. In contrast, patients with severe or very severe pain were more likely to describe the pain

Table 2 Effect on daily activities and quality of life

	Mild (n = 38)*	Severe (n = 22)
General activity	2·29 (1·61, 2·97)	6·55 (5·54, 7·55)
Mood	1·78 (1·14, 2·43)	6·45 (4·94, 7·97)
Walking	2·34 (1·55, 3·13)	6·05 (4·80, 7·29)
Work	2·59 (1·73, 3·45)	6·45 (5·26, 7·65)
Relationships	1·42 (0·69, 2·15)	5·05 (3·40, 6·70)
Sleep	1·32 (0·76, 1·92)	6·41 (5·33, 7·49)
General enjoyment of life	2·32 (1·50, 3·13)	7·14 (5·97, 8·30)

Values are mean difference (95 per cent confidence interval). *One patient did not complete this section

Table 3 Descriptors of pain

	Mild (n = 38)*	Severe (n = 22)
Neuropathic		
Aching	15	12
Burning	3	4
Cutting	0	2
Electric shock	0	0
Itching	1	1
Prickling	3	1
Shooting	7	4
Stabbing	7	7
Tingling	3	2
Nociceptive		
Drilling	0	0
Gnawing	5	5
Pounding	1	1
Pulling	3	11†
Sickening	2	4
Tender	5	8‡
Throbbing	5	12†
Three or more words used	6	13†

*One patient did not complete this section. †P = 0·001, ‡P = 0·027 *versus* mild (Fisher's exact test)

using multiple terms which indicated that the character of the pain was both neuropathic and nociceptive (*Table 3*). Numbness was present in significantly more patients in the severe or very severe pain group (18 of 22 *versus* 18 of 38; P < 0·001) (*Table 4*). In addition the numbness was more extensive in these patients and likely to involve both the groin and thigh.

Other chronic pain conditions

Patients in the severe–very severe group were significantly more likely to suffer from other chronic pain conditions than those in the very mild–mild group (20 of 22 *versus* 23 of 37; P = 0·016). The most common illness was chronic back pain in both groups, and significant numbers also suffered from headache and irritable bowel syndrome (*Table 5*). Other conditions that caused chronic pain in these patients included pain from scars elsewhere in the body and peptic ulcer disease.

Table 4 Numbness

	Mild (n = 38)*	Severe (n = 22)	All patients (n = 60)
Groin	12	5	17
Thigh	1	0	1
Both	5	13	18

*One patient did not complete this section

Table 5 Other chronic illness

	Mild (n = 37)*	Severe (n = 22)	All patients (n = 59)
Backache	17	17	34
Headache	7	6	13
Irritable bowel	4	7	11
Other	5	3	8

*Two patients did not complete this section

Discussion

Severe or very severe pain was reported in 3 per cent of patients at 3 months after groin hernia repair in Scotland. At a median follow-up of 30 months 26 per cent still reported severe or very severe pain which had profound effects on daily activities and quality of life. Only 29 per cent of the group reported no pain, while in 45 per cent the pain had become very mild or mild. Almost half of the patients had sought treatment for their pain by visiting their general practitioner, surgeon or a pain clinic.

This is the second study that has examined chronic pain after hernia repair on a nationwide basis. In a Danish study[2] that reviewed 1652 patients operated on for a groin hernia over a 2-month period, 29 per cent reported pain at 1 year after operation. Although 11 per cent reported that the pain affected leisure activities, only 4 per cent sought or received medical treatment while 3 per cent reported that the pain was moderate or severe. In the Medical Research Council randomized trial[5] of laparoscopic *versus* open groin hernia repair 29 and 37 per cent of patients respectively had groin pain at 1 year. The respective figures for severe or very severe pain were 4 and 2 per cent. In a subset of 379 patients operated on under the care of one surgeon from the same study[7] and followed clinically for a median of 5 years, six (2 per cent) required referral to a pain clinic for severe or very severe pain. In three of these patients the pain resolved while two still had mild pain and one had died from bronchogenic cancer.

This is the first population-based study to determine the long-term outcome of patients reporting severe or very severe pain after repair of a groin hernia. As in a previous study[7], the indications are that this resolves or becomes mild or very mild in the majority of patients. Around 25 per cent continue to have severe or very severe pain, similar to the results of a previous study retrospective study[13] in which 30 per cent of those with pain 3 months after operation reported moderate or unbearable pain at a median of 43 months after operation.

The cause of chronic groin pain after hernia repair is thought to be related to nerve injury. This is supported by the high frequency of sensory symptoms and numbness in these patients[2]. However, other factors such as tissue injury may be important. The character and distribution pattern of pain suffered by these patients is similar to that observed in athletes with groin injury[14], in whom the source of pain is thought to be muscular or ligamentous injury. The role of non-absorbable material, either sutures or mesh, should also be considered. While there have been no comparative studies in hernia repair, use of absorbable suture materials has consistently been shown to cause less chronic pain after abdominal wall closure than non-absorbable materials[15–17].

Whatever the mechanism of chronic pain following hernia repair it would seem that the individual's perception of pain may also be important. Patients who go on to suffer chronic pain are more likely to have complained of pain from the hernia before operation than those who have no postoperative pain[7]. In addition, this study indicates that they are more likely to suffer from other chronic pain conditions compared with the normal population. In population-based studies[18,19] 27–39 per cent of patients surveyed indicated that they had had back pain in the previous week or month; the respective figures for patients with very mild–mild or severe–very severe pain were 46 and 77 per cent. An alternative explanation for the high incidence of back pain in the severe pain group may be related to placing excessive strain on the back muscles in an effort to protect the groin. Further studies on the interrelationship between these conditions and the psychological profile of the patients are required.

The present study may underestimate the frequency of severe or very severe pain following hernia repair in that some patients will have developed this problem after the first questionnaire was sent out. In a study by Callesen *et al.*[3] moderate or severe pain at 4 weeks was a significant predictor of the same type of pain at 1 year; despite this around half of the patients who had moderate or severe pain at 1 year had no or light pain at 4 weeks after operation. In a similar study[7], in which 379 patients were followed for a median of 5 years after groin hernia repair, 25 per cent of patients who had chronic pain developed it after the 1-year follow-up period. Most, however, were worried that the repair had broken down and when reassured that this was not the case their symptoms resolved.

Over two-thirds of patients who complain of severe or very severe chronic groin pain at 3 months after groin hernia repair still have pain 2–3 years later. While the mechanism of this pain is unclear, counselling patients on its probability before operation is required, while early referral to an established pain clinic should be considered for those who develop this debilitating problem. Finally, clinical trials comparing the use of absorbable with non-absorbable sutures and meshes for groin hernia repair should be undertaken.

Acknowledgements

This study was funded by the Scottish Executive.

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Pain from primary inguinal hernia and the effect of repair on pain

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Background: No previous study has attempted to quantify pain from a primary inguinal hernia. The aim of this study was to quantify patients' pain from inguinal hernia at rest and on moving, and to assess the effect of hernia repair on the pain.

Methods: Linear analogue pain scores at rest and on moving were recorded before operation and at 1 year after surgery in a consecutive series of patients undergoing elective repair of a primary inguinal hernia.

Results: During the study period 323 patients underwent inguinal hernia repair. Eighty-six patients (26·6 per cent) recorded no pain at rest from the hernia, and 174 (53·9 per cent) had mild pain only (score less than 10). On moving, 53 patients (16·4 per cent) had no pain and 137 (42·4 per cent) had mild pain on moving. Only 1·5 per cent experienced severe pain (score greater than 50) at rest, and 10·2 per cent had severe pain on moving. There was no association between pain and hernia type, direct or indirect, or patient occupation. One year after operation only 24·5 per cent of patients had no pain from the hernia repair site at rest, and 21·6 per cent had no pain from the site on moving. Overall there was a significant reduction in pain score at rest (mean(s.e.m.) decrease from baseline −2·9(1·2), $P = 0{\cdot}019$) and on moving (− 9·2(1·8), $P = 0{\cdot}001$) compared with preoperative values, and this was due mainly to the large effect observed in patients with high preoperative values. Patients who had no pain at rest before operation had significant pain scores at rest at 1 year ($P = 0{\cdot}001$).

Conclusion: Clinical trials are required to evaluate hernia repair in patients with an asymptomatic inguinal hernia. Results from such trials should help to determine whether repair is the treatment of choice for these patients.

Paper accepted 8 May 2002

British Journal of Surgery 2002, 89, 1315–1318

Introduction

Inguinal hernia repair is one of the most common operations performed in general surgery, with rates of repair ranging from 10 per 10 000 in the UK to 28 per 10 000 in the USA[1]. Recent evidence indicates that up to one-third of all patients undergoing hernia repair have a painless hernia that has little or no effect on work or leisure activities[2]. In contrast to this, 3–6 per cent of patients will have severe pain, and more than 30 per cent will have mild pain, 1 year after hernia repair[3–5]. This pain persists for many years and has significant effects on work and leisure activities[6]. The aim of this study was to quantify patients' pain from inguinal hernia at rest and on moving, and to assess the effect of hernia repair on the pain.

Patients and methods

All patients undergoing elective repair for a primary inguinal hernia who were admitted to the care of one surgical unit between January 1998 and October 2000 were entered into the study. Patients were asked to complete a linear analogue pain score of the degree of pain caused by the hernia at rest and on movement. Pain scores were recorded on a 100-mm line by a single observer 24 h before operation; 0 represented no pain and 100 the most severe pain. Pain scores related to the hernia repair site were repeated at 1 year and all patients were examined for clinical evidence of hernia recurrence at that visit. Arbitrarily, a score of less than 10 was graded as mild pain, a score of 10–50 as moderate pain and a score of more than 50 as severe pain.

Table 1 Patient characteristics

	No. of patients (n = 323)
Age (years)	
> 50	201 (62·2)
≤ 50	122 (37·8)
Sex	
M	306 (94·7)
F	17 (5·3)
Site	
Right	170 (52·6)
Left	127 (39·3)
Bilateral	26 (8·0)
Type	
Direct	176 (54·5)
Indirect	147 (45·5)
Occupation	
Moderate manual	57 (17·6)
Heavy manual	53 (16·4)
Sedentary	72 (22·3)
Retired	141 (43·7)

Values in parentheses are percentages

Statistical analysis

Within- and between-group differences were analysed with a t test. Where there was sufficient doubt about the validity of parametric assumptions (assessed graphically), a Wilcoxon or Mann–Whitney U test was performed.

Results

A total of 323 patients with a primary inguinal hernia underwent an open tension-free mesh repair during the study period. Characteristics of the patient group are shown in *Table 1*. The majority had no pain from the hernia, or only mild pain, at rest (80·5 per cent) or on moving (58·8 per cent). Only 1·5 per cent experienced severe pain at rest, and 10·2 per cent had severe pain on moving (*Table 2*).

Patients older than 50 years were significantly more likely to have pain associated with the hernia than their younger counterparts ($P < 0{\cdot}01$). Surprisingly there was no association between hernia type, direct or indirect, or occupation and the presence of pain at the hernia site. Although women were more likely to have pain at rest and on moving, this effect was not significant and is likely to reflect the small number of women (17) in the study (*Table 3*).

At 1 year after operation 204 patients (63·2 per cent) returned for clinical review and completed pain scores from the hernia repair site at rest and on moving (*Table 4*). Only 24·5 per cent of patients had no pain at rest, and only 21·6 per cent had no pain on moving. While, overall, the group showed a significant reduction in pain scores at rest ($P = 0{\cdot}019$) and on moving ($P = 0{\cdot}001$) compared with preoperative levels, this was due mainly to the large effect observed in patients with high preoperative values (*Table 5*). In contrast, patients who had no pain at rest before operation had significant pain scores at rest at 1 year ($P = 0{\cdot}001$). No patient had a recurrence of the hernia or other chronic complication at the 1-year follow-up visit.

Table 2 Severity of pain in 323 patients

	At rest	On moving
No pain (0)	86 (26·6)	53 (16·4)
Mild (< 10)	174 (53·9)	137 (42·4)
Moderate (10–50)	58 (18·0)	100 (40·0)
Severe (> 50)	5 (1·5)	33 (10·2)

Values in parentheses are percentages

Table 3 Pain scores in relation to patient characteristics

	At rest	On moving
Age (years)		
> 50	7·5(11·9)	18·5(23·8)
≤ 50	6·7(13·0)	14·4(19·6)
Sex		
M	6·8(12·2)	16·2(21·9)
F	12·0(14·6)	28·7(29·2)
Site		
Right	6·7(12·4)	18·2(23·4)
Left	7·9(13·1)	15·1(20·3)
Bilateral	5·1(7·5)	16·5(26·1)
Type		
Direct	7·4(12·8)	16·4(22·5)
Indirect	6·7(11·8)	17·3(22·5)
Occupation		
Moderate manual	9·0(14·7)	17·4(20·4)
Heavy manual	5·9(13·7)	16·0(19·8)
Sedentary	5·8(9·6)	18·1(25·1)
Retired	7·7(12·5)	16·7(23·0)

Values are mean(s.d.)

Table 4 Severity of pain 1 year after hernia repair in 204 patients

	At rest	On moving
No pain (0)	50 (24·5)	44 (21·6)
Mild (< 10)	128 (62·7)	114 (55·9)
Moderate (10–50)	22 (10·8)	41 (20·1)
Severe (> 50)	4 (2·0)	5 (2·5)

Values in parentheses are percentages

Table 5 Effect of operation on preoperative pain score

	No. of patients	At rest	On moving
All patients	204	– 2·9(1·2)*	– 9·2(1·8)*
Preoperative score at rest			
0	40	1·8(0·3)*	– 0·3(1·6)
> 10	37	– 22·8(3·7)*	– 32·2(4·8)*

Values are mean(s.e.m.). *$P \leq 0{\cdot}01$ *versus* baseline value (t test)

Discussion

This study demonstrates that most primary inguinal hernias repaired electively are painless or cause the patient only mild pain. The decision to classify mild pain as a score of less than 10 in this study was arbitrary and is lower than that suggested by some workers[7]. The findings that almost 60 per cent of patients indicated that the hernia was painless or caused mild pain only on movement, while about 80 per cent had no pain or mild pain at rest, are therefore conservative. This remains so even if acute inguinal hernias causing severe pain are included, as they account for only 5 per cent of all inguinal hernias treated in the region[8].

At 1-year follow-up, patients who had no pain at rest from the hernia before operation reported significant pain scores from the hernia repair site. Although these scores were low, the finding goes some way to explaining the relatively low level of satisfaction reported by patients following hernia repair[5]. When asked about change in day-to-day life 1 year after hernia repair in one study[5], almost 30 per cent of patients reported no change while 5 per cent were slightly or much worse after operation. A further 12 per cent reported that hernia repair made day-to-day life only slightly better, and 55 per cent were much better.

The presence of pain in patients who were asymptomatic from the hernia in the first place is worrying and leads one to question whether these people should have had a hernia repair in the first instance. The most common reason for recommending hernia repair in patients is the risk of incarceration or strangulation. However, it is known that the probability of the latter event occurring is rare and is observed in only one in every 300–400 patients with an inguinal hernia[2,9]. Moreover, patients who develop this complication will often not be aware that they have had a hernia or will be sufficiently ill from other co-morbid illness that they will have been turned down for elective repair[10]. The latter group is likely to be the main cause for the high mortality rate associated with emergency hernia surgery presenting with an incarcerated or strangulated hernia in the face of end-stage cardiorespiratory disease or cancer[11,12].

Interestingly there was no association in the present study between hernia type (direct or indirect) or the patient's occupation (sedentary or heavy manual work) and pain at the hernia site. Conventional teaching would suggest that indirect hernias are more likely to be symptomatic, while the presence of a hernia in someone who does heavy manual work might be thought of as a significant inconvenience. Indeed, this group might be expected to register high pain scores on moving. If anything, the trend in this study was for these patients to have the lowest pain scores at rest and on moving.

Results from this study indicate that repair has less effect than might be expected on the mild pain caused by an inguinal hernia. Pain scores at rest and moving were reduced to only about half the level before operation. Furthermore it is disappointing that there was not a significant increase in the number of patients who recorded no pain at rest or moving 1 year after the operation. The major effect of hernia repair appears to be to convert those with moderate or severe pain on moving to mild pain on moving. One of the drawbacks of the present study is that other quality-of-life issues such as the effect of a hernia on social or sexual activity has not been examined. In a previous study[2], however, the authors showed that leisure activities were affected in only 29 per cent of patients with an inguinal hernia, while only 13 per cent had to take time off work because of the hernia. Further studies are required in this area, with a more detailed look at these factors, particularly in patients who reported no pain at rest or on moving.

Not surprisingly, this study demonstrated that the patients most likely to benefit from hernia repair were those who had moderate to severe pain in the first instance. In contrast, it is clear that some patients with no pain from the hernia were made worse by repair. Clinical trials are required to determine whether repair is the treatment of choice for patients with an asymptomatic inguinal hernia.

Acknowledgements

This work was funded by the Scottish Executive.

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Original article

Effect on outcome of early intensive management of geriatric trauma patients

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Background: Despite significant injuries elderly patients (aged 70 years or more) often do not exhibit any of the standard physiological criteria for trauma team activation (TTA), i.e. hypotension, tachycardia or unresponsiveness to pain. As a result of these findings the authors' TTA criteria were modified to include age 70 years or more, and a protocol of early aggressive monitoring and resuscitation was introduced. The aim of the present study was to assess the effect of the new policy on outcome.

Methods: This trauma registry study included patients aged 70 years or more with an Injury Severity Score (ISS) greater than 15 who were admitted over a period of 8 years and 8 months. The patients were divided into two groups: group 1 included patients admitted before age 70 years and above became a TTA criterion and group 2 included patients admitted during the period when age 70 years or more was a TTA criterion and the new management protocol was in place. The two groups were compared with regard to survival, functional status on discharge and hospital charges.

Results: There were 336 trauma patients who met the criteria, 260 in group 1 and 76 in group 2. The two groups were similar with respect to mechanism of injury, age, gender, ISS and body area Abbreviated Injury Score. The mortality rate in group 1 was 53·8 per cent and that in group 2 was 34·2 per cent ($P = 0{\cdot}003$) (relative risk (RR) 1·57 (95 per cent confidence interval 1·13 to 2·19)). The incidence of permanent disability in the two groups was 16·7 and 12·0 per cent respectively ($P = 0{\cdot}49$) (RR 1·39 (0·59 to 3·25)). In subgroups of patients with an ISS of more than 20 the mortality rate was 68·4 and 46·9 per cent in groups 1 and 2 respectively ($P = 0{\cdot}01$) (RR 1·46 (1·06 to 2·00)); 12 of 49 survivors in group 1 and two of 26 in group 2 suffered permanent disability ($P = 0{\cdot}12$) (RR 3·18 (0·77 to 13·20)).

Conclusion: Activation of the trauma team and early intensive monitoring, evaluation and resuscitation of geriatric trauma patients improves survival.

Paper accepted 11 June 2002

British Journal of Surgery 2002, **89**, 1319–1322

Introduction

In a previous study it was reported that elderly trauma patients (aged 70 years or more) often fail to exhibit the standard haemodynamic and respiratory trauma team activation (TTA) criteria, even in the presence of severe, life-threatening injuries[1]. As a result of these findings the authors' TTA criteria were modified to include age of 70 years or more. In addition, a protocol of early intensive monitoring and resuscitation and early surgical intensive care unit (ICU) admission was introduced. The purpose of the present study was to assess the effect of the new policy on mortality rates and hospital charges.

Patients and methods

This was a trauma registry-based study performed at the Los Angeles County and University of Southern California Medical Center, a level I academic trauma centre. The study included all patients who were 70 years old or more, met the Los Angeles County trauma centre and trauma registry

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

criteria, and were admitted between January 1993 and August 2001. Interhospital transfers and patients not meeting trauma registry criteria were excluded from the study. Patients who have had ground-level falls, even with major fractures, are not included in the trauma registry. The trauma attending (consultant) on call is in house on a 24-h basis, leads all trauma team activations, and directly supervises all procedures performed in the operating room. The trauma team responds within 5 min of TTA and is usually present in the resuscitation room before the patient arrives. The team includes attendings and senior residents from the Division of Trauma and Critical Care and the Department of Emergency Medicine. TTA patients receive the highest priority with regard to investigations, ICU admission and operating rooms. They are monitored continuously in the emergency room and radiology department by senior resident or attending staff.

An EXCEL (Microsoft Corporation, Redmond, Washington, USA) database was created for the purpose of this study and included age, gender, mechanism of injury, Abbreviated Injury Score (AIS) for each body area, Injury Severity Score (ISS), Revised Trauma Score, survival status, duration of ICU and hospital stay, functional status on discharge and hospital charges.

The study patients were divided into two groups: group 1 included patients admitted between January 1993 and February 2000 when age 70 years or more was not a TTA criterion; group 2 included patients admitted from March 2000 to August 2001, when age 70 years or greater was an absolute TTA criterion and a policy of early advanced haemodynamic and tissue perfusion monitoring, resuscitation and ICU admission was in place. The TTA criteria for the two intervals are shown in *Table 1*.

In group 2 liberal use was made of non-invasive cardiac output monitoring and tissue perfusion with non-invasive measurement of transcutaneous oxygen and carbon dioxide, early intubation of the patient in the emergency room before going to the radiology department, admission to the ICU (even for fairly minor injuries) and insertion of a Swan–Ganz catheter.

Comparisons between the two groups were made with the χ^2 test for categorical variables and the *t* test for continuous variables.

Table 1 Trauma team activation criteria applied during the two study periods

1	Systolic blood pressure < 90 mmHg or pulse > 120/min
2	Respiratory rate < 10 or > 29 breaths/min
3	Unresponsiveness to pain
4	Emergency physician judgement
5	Age ≥ 70 years

Group 1 (January 1993 to February 2000): TTA criteria 1–4; group 2 (March 2000 to August 2001): TTA criteria 1–5. Also liberal early advanced haemodynamic and tissue perfusion monitoring, early intubation in the emergency room, early admission to the intensive care unit and insertion of a Swan–Ganz catheter

Table 2 Epidemiological data of patients aged 70 years or more with an Injury Severity Score greater than 15

	Group 1 (*n* = 260)	Group 2 (*n* = 76)	*P**
Mean age (years)	77	78	
Men	156 (60·0)	42 (55·3)	0·51
Trauma type			
Blunt	250 (96·2)	71 (93·4)	0·48
Penetrating	10 (3·8)	5 (6·6)	0·48
AIS ≥ 3			
Head	204 (78·5)	58 (76·3)	0·75
Chest	79 (30·4)	21 (27·6)	0·67
Abdomen	48 (18·3)	19 (25·0)	0·25
Skeletal system	59 (22·7)	13 (17·1)	0·34
Mean(s.d.) ISS	25(10)	24(7)	0·45

Values in parentheses are percentages unless otherwise indicated. AIS, Abbreviated Injury Score; ISS, Injury Severity Score. *χ^2 test

Results

During the study period there were 1080 patients aged 70 years or more who were admitted to the trauma centre. The 336 patients with an ISS greater than 15 formed the group for outcome analysis.

There were 260 patients in group 1 and 76 patients in group 2. The two groups were similar with regard to mechanisms of injury, age, gender, AIS and ISS (*Table 2*). The most commonly severely injured body area with an AIS of 3 or more was the head (78·0 per cent) followed by the chest (29·8 per cent), the skeletal system (21·4 per cent) and the abdomen (19·9 per cent). The incidence of these injuries in the two groups was similar (*Table 2*). The mean ISS was 25 in group 1 and 24 in group 2 ($P = 0{\cdot}45$).

The overall mortality rate was 49·4 per cent (166 of 336). The mortality rate in group 2 was significantly lower than that in group 1 (34·2 *versus* 53·8 per cent; $P = 0{\cdot}003$) (*Table 3*). The relative risk (RR) of death was 1·57 (95 per cent confidence interval 1·13 to 2·19). The incidence of permanent disability in survivors was 12·0 per cent in group 2 and 16·7 per cent in group 1 ($P = 0{\cdot}49$) (RR 1·39 (0·59 to 3·25)). The duration of ICU and hospital stay was similar in both groups, although there was a trend toward higher hospital charges in group 2 (*Table 3*). Overall, 22·2 per cent of survivors in group 2 and 20·5 per cent in group 1 were

Table 3 Outcome for patients aged 70 years or more with an Injury Severity Score above 15

	Group 1 (*n* = 260)	Group 2 (*n* = 76)	*P*†
Death	140 (53·8)	26 (34·2)	0·003
Permanent handicap*	20 (16·7)	6 (12·0)	0·49
Mean(s.d.) ICU stay (days)	5·2(9·8)	4·5(10·1)	0·61
Mean(s.d.) hospital stay (days)	10·2(13·3)	10·7(13·8)	0·77
Hospital charges (US $)	49 644	64 249	0·20

Values in parentheses are percentages unless otherwise indicated. *In survivors. ICU, intensive care unit †χ^2 test

Table 4 Outcome for patients aged 70 years or more with an Injury Severity Score above 20

	Group 1 (*n* = 155)	Group 2 (*n* = 49)	*P*†
Death	106 (68·4)	23 (46·9)	0·01
Permanent handicap*	12 (24·5)	2 (7·7)	0·12
Mean(s.d.) ICU stay (days)	4·9(8·3)	3·5(6·0)	0·26
Mean(s.d.) hospital stay (days)	9·6(12·9)	9·1(8·9)	0·83
Hospital charges (US $)	45 745	53 327	0·52

Values in parentheses are percentages unless otherwise indicated. *In survivors. ICU, intensive care unit †χ^2 test

transferred to a rehabilitation centre or skilled nursing facility.

There were 204 patients with an ISS above 20 in whom the overall mortality rate was 63·2 per cent (129 deaths). The mortality rate in group 2 was significantly lower than that in group 1 (46·9 *versus* 68·4 per cent; P = 0·01) (RR 1·46 (1·06 to 2·00)). Twelve of 49 survivors in group 1 and two of 26 in group 2 suffered permanent disability (P = 0·12) (RR 3·18 (0·77 to 13·20)). Other outcome variables, such as ICU and hospital stay and hospital charges, were not significantly different (*Table 4*).

Discussion

Geriatric patients who suffer trauma have significantly higher mortality and complication rates, and a longer hospital stay, than younger patients. In a previous study from this centre the overall mortality rate in a series of 883 trauma patients aged 70 years or more was 24 per cent, compared with 7·6 per cent in a group of 24 958 patients younger than 70 years of age[1]. Other series have reported overall mortality rates ranging from 15 to 30 per cent in geriatric trauma patients and from 4 to 8 per cent in younger patients[2]. The most important reason for this high mortality rate is the limited physiological reserve in elderly patients, which may turn even a moderate stress into a life-threatening condition.

Another complicating factor is the often delayed or inadequate resuscitation and treatment resulting from a misleading clinical picture of stability on admission. Tachycardia may be absent despite the presence of severe injuries, because of the inherent inability of the cardiovascular system of elderly patients to respond to endogenous or exogenous signals or because of cardiac medications such as beta-blockers. A 'normal' blood pressure or mild hypotension in patients with hypertensive disease may in reality signify significant hypotension with tissue hypoperfusion. In a previous study[1] it was reported that 63 per cent of geriatric trauma patients with an ISS above 15 and 25 per cent of those with an ISS greater than 30 did not have any of the standard haemodynamic criteria for TTA. Many of these patients decompensate easily and without warning, often in the radiology suite or non-monitored areas, making successful resuscitation and survival less likely. The safety margin between hypovolaemic shock and fluid overloading with cardiac failure is narrow. Deterioration and failure of the respiratory system in elderly patients, especially those with rib fractures or lung contusion, may occur rapidly and with little warning. Cardiac complications account for 30 per cent and respiratory complications for 16 per cent of deaths in geriatric trauma patients[1]. Other factors that might contribute to the increased mortality rate in elderly trauma patients include the use of diuretics, which results in chronic intravascular depletion and poor tolerance of any blood loss, and anticoagulants, which predispose to intracranial haematomas and aggravate any bleeding.

Many of these problems can be prevented by early and continuous monitoring and resuscitation by the trauma team and early admission to the ICU. Scalea *et al.*[3] demonstrated improved survival in geriatric patients undergoing early invasive monitoring. With the development of new non-invasive techniques, cardiac output and tissue perfusion can be monitored early and reliably soon after admission to the emergency department[4,5].

The early presence in the emergency room of the trauma team led by an experienced trauma surgeon results in improved outcomes in severely injured patients. However, owing to limited resources and costs, activation of the trauma team needs to be rationalized and used for subgroups of patients who are most likely to benefit from the activation. The traditional TTA criteria used by most trauma centres and recommended in the Resources for Optimal Care of the Injured Patient (Amendment 17, June 2000)[6] do not include old age. The present study has demonstrated that the introduction of old age as a TTA criterion, and early aggressive monitoring and resuscitation, resulted in a significant improvement in outcome. On the basis of these results, age 70 years or greater has now become a permanent TTA criterion and trauma quality improvement filter in the authors' programme.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All letters will be reviewed and, if approved, appear on the website. A selection of these will be edited and published in the Journal. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk.*

Randomized clinical trial of the effectiveness of emergency day surgery against standard inpatient treatment (*Br J Surg* 2002; 89: 423–7)

Sir

The authors of this study should be applauded for their attempt to rationalize the use of inpatient beds for minor and intermediate general surgery emergencies. However, 93 per cent of patients in the study presented with an abscess. Does this reflect the normal distribution of emergency admissions? The authors do not report the method of randomization, which is imperative to avoid bias. The number and types of exclusions within the suitable patient group were also not included. The authors conclude that cost savings are made without detriment to patient care. As a large pilot study had been undertaken, a cost utility analysis could have been used as a primary outcome rather than using multiple endpoints. One-third of patients in the day surgery group were treated on an inpatient ward. This may reduce the savings estimated by the authors. The only conclusion that can be made is that patients with a simple abscess can be treated without urgent admission. Rather than placing patients on unpredictable gaps in an operating schedule, perhaps the best rationale would be to place these patients first on the emergency list of the next working day. This would allow planned admission and discharge from a day unit bed.

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Management of intermittent claudication (*Br J Surg* 2002; 89: 529–31)

Letter 1

Sir

In this excellent leading article it was suggested that the use of statins might be indicated due to their beneficial effects on atherosclerosis, but that results of further studies were awaited. The Oxford Heart Protection Study is the largest trial of lipid-lowering therapy in the world[1]. The effect of statin therapy in a cohort of over 20 000 patients was examined and showed some striking benefits. Most significantly, it showed that in 1000 patients, whose only risk factor was peripheral arterial disease, treatment with a statin could prevent 70 major vascular events. This represents the best evidence yet that statin therapy is indicated in all patients with peripheral vascular disease, regardless of other risk factors.

With this evidence in mind, we performed an audit of patients attending a vascular outpatient clinic to find out what proportion had been prescribed a statin. Worryingly, only 28 per cent of patients with peripheral arterial disease were taking a statin, despite 35 per cent being hypercholesterolaemic. Indeed, nearly all of the patients in the audit who were taking a statin were doing so for their hypercholesterolaemia, with only one patient prescribed a statin for reasons other than this. There is now overwhelming evidence that statins exert beneficial pleiotropic effects unrelated to their lipid-lowering properties[2]. Prescription of these drugs for patients that would benefit from them, however, is still lagging far behind.

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Letter 2

Sir

Professor Shearman has not mentioned one important technique in the management of intermittent claudication – subintimal angioplasty. The technique has been well established in our unit and is being practised in a number of other centres[1]. The reported primary symptomatic patency rate for femoropopliteal occlusions is 61 per cent[2] and even in isolated infragenicular vessels the clinical success rate is 80 per cent after 3 years[3]. This success is comparable to bypass surgery, where a patency rate of 55 per cent is noted after 2 years[4]. Even though transluminal angioplasty is being practised in many centres the results of the procedure are poor, with occlusions of more than 5 cm and stenotic regions of more than 10 cm. In contrast, subintimal angioplasty can be performed over almost any length and the new channel is often wider than the original[2]. There remains the objection that there has been no randomized prospective comparison of subintimal angioplasty and bypass surgery. As surgery is not used for most claudicants, and because of the high mortality rate of distal grafts for rest pain, it is almost unethical to subject certain patients to surgery with its associated morbidity. In our centre subintimal angioplasty is the first line of treatment for rest pain and for claudication if conservative management fails. More interventional radiologists should be trained in the procedure but they will still have to work in conjunction with the surgeons to deal with the acute complications of this, and any, endovascular procedure.

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Letter 3

Sir

This article did not classify claudicants by the anatomical distribution of the underlying arterial disease. The risks, benefits of exercise, angioplasty and surgery are clearly different in patients with suprainguinal *versus* infrainguinal disease. Two randomized trials that compared percutaneous transluminal angioplasty (PTA) with exercise failed to show any long-term advantage from PTA. However, both these trials predominately involved patients with femoropopliteal lesions, not iliac where the patency rates are over 20 per cent better[1,2]. Certainly the TransAtlantic Inter-Society Consensus document[3] recommends angioplasty for short proximal iliac lesions where patency rates of over 70 per cent are documented over 2 years. Angioplasty itself carries a complication risk (less than 1 per cent mortality rate and less than 5 per cent limb loss). The identification of a suprainguinal lesion primarily by duplex rather than diagnostic angiography further reduces the complication rate. Chetter *et al.*[4] have demonstrated that patients with unilateral claudication undergoing PTA of a solitary iliac lesion have the most marked quality of life benefits; 12 months after PTA they have a quality of life approaching that of an age-matched population.

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Author's reply

Sir

I entirely agree about the importance of treatment of hyperlipidaemia and the yet to be characterized benefits of risk factor management in patients with peripheral vascular disease. However, many of these benefits have long been recognized and yet are still poorly addressed. I was dismayed to find in a recent audit in my own unit in Southampton that 32 per cent of patients awaiting carotid endarterectomy had untreated hypercholesterolaemia. The real challenge seems to be how to transfer the knowledge and enthusiasm that many vascular teams have for risk factor management to the individual patient. I believe we need new ways of achieving this, including clinics run in conjunction with primary care to support and encourage patients with peripheral vascular disease make changes in their lifestyle and health that could significantly improve what its otherwise a dismal prognosis.

The success of subintimal angioplasty in Leicester has been widely reported, but other groups have been unable to replicate their results, particularly in the longer term[1]. Despite this concern I think Ingle and Bell have overlooked the main issue of the role of revascularization techniques in general for the treatment of claudication. Until this is clearly established with sound data there seems little point in arguing about which is the best interventional treatment. Furthermore, in their letter they confusingly mix results of treatment for critical limb ischaemia with claudication. These are entirely different in their prognosis for the patient. For a patient with claudication, what matters is their functional improvement, not whether their angioplasty site is patent. The fact remains that there is currently no evidence to show that a patient with intermittent claudication benefits from angioplasty (subintimal or conventional) above other non-interventional treatments.

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1 McCarthy RJ, Neary W, Roobottom C, Tottle A, Ashley S. Short-term results of femoropopliteal subintimal angioplasty. *Br J Surg* 2000; **87:** 1361–5.

Randomized clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure (*Br J Surg* 2002; 89: 413–17)

Sir

The sample size for this study ($n = 26$) was calculated based on an assumption that headache would be experienced in 10 per cent of patients in the diltiazem hydrochloride (DTZ) group. However, the results show that over 25 per cent experienced headaches, making the sample size inadequate. Therefore this study should be regarded as a pilot study for a larger study to arrive at valid conclusions. Analyses were done on an 'intention to treat' basis ($n = 29$ and $n = 31$ for glyceryl trinitrate (GTN) and DTZ, respectively) rather than on patients who completed treatment ($n = 26$ and $n = 22$, respectively). Although the 'intention to treat' basis is more logical in larger numbers, it makes a considerable difference when analysing small numbers. When the analysis is carried out on patients who actually completed treatment, the statistical significance disappears both with regard to any side-effects ($P = 0{\cdot}12$) or headache ($P = 0{\cdot}08$), which is the primary endpoint (Fisher's exact test). Healing rates were calculated on all 29 patients in the GTN group and on 31 in the DTZ group at 8 weeks. It is not possible to do this when one and two patients were lost to follow-up in each group, respectively, in addition to an unspecified number of patients whose follow-up was completed by post or telephone without clinical examination. Recurrence rates at 12 weeks are quoted but the pain scores at 12 weeks are not depicted in the graph (*Fig. 2*), which are the secondary endpoints. Moreover, the follow-up mentioned in the initial design is at 9 weeks rather than 8 weeks as is shown in the graph. Scrutinizing *Fig. 2* shows an appreciable difference in the pain scores between the groups at 6 and 8 weeks in favour of the GTN group, which needs further validation by comparing medians and interquartile ranges, rather than mean(s.e.m.) which is more appropriate for a matched non-parametric test (Wilcoxon test). There may be statistical significance favouring the GTN group.

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Impact of diagnostic laparoscopy on the management of gastric cancer: prospective study of 120 consecutive patients with primary gastric adenocarcinoma (*Br J Surg* 2002; 89: 471–5)

Letter 1

Sir

This paper claims to be the first study to evaluate prospectively the use of selective staging laparoscopy for gastric cancer, but previously published reports[1–3] already refer to selection algorithms, and many of these described prospective studies. Our reports[1,4] advocated the use of the low-cost technique of immediate preoperative laparoscopy. When prospectively compared with conventional staging procedures this simple technique had the highest sensitivity for peritoneal dissemination and a significantly better accuracy for T3/T4 tumours[1]. The most striking difference with other published data is that in Lehnert *et al.*'s series the selective application of laparoscopy had a failure rate of almost 25 per cent, since in four of 15 cases it missed the peritoneal seeding that was evident at open exploration. Lehnert *et al.*'s conclusions are based on an experience of 15 staging laparoscopic explorations accomplished over a 2-year interval, whilst the majority of the published reports refer to greater numbers[2–4]. The results of the study by

Lehnert *et al.*, indicating a limited role for laparoscopic staging of gastric cancer, should be interpreted with caution.

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Letter 2

Sir

I agree that the findings from the study support the authors' conclusions; however, there are some issues I would like to highlight. It is well known that laparoscopy is beneficial in the diagnosis of advanced disease. There is a 20 per cent incidence of peritoneal metastasis in stage T3 and a much greater incidence in T4 gastric cancer. It is difficult to identify these patients beforehand and in the western world, where the majority of the disease is advanced, it may be necessary to laparoscope most patients. It is worth mentioning that even patients with stage T2 disease could have liver metastasis picked up on laparoscopy. There is a school of thought that laparoscopy provides the opportunity for a 'trial of anaesthesia' for patients awaiting potentially curative major gastric resection. The anaesthetist would be able to pick up haemodynamic instability during the short period of anaesthesia and could quantify the risks to the patient; this may help to modify the treatment plan. In addition, laparoscopic gastrojejunostomy is feasible in patients with advanced disease, thereby avoiding laparotomy with its attendant problems.

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Authors' reply

Sir

We agree with Dr D'Ugo that reports on staging laparoscopy should be read carefully. Most trials, including the prospective studies quoted in our article, and the older study by D'Ugo *et al.*, do not report on all patients with gastric cancer, but only on a selected group. This may result in serious bias. To the best of our knowledge our study is the first to document prospectively all patients with a diagnosis of gastric cancer, as stated in the manuscript. It is also important to understand that we did not intend to study the diagnostic accuracy of laparoscopy, but the potential benefit of its selective use for decision-making in gastric cancer. Of course the failure rate could have been made to look better had all patients been subjected to laparoscopy. Such improvement would have come at the expense of many unnecessary laparoscopies, which did not alter the decision to perform a laparotomy. The absolute number of false-negative laparoscopies would have been the same. We do not agree that an invasive diagnostic procedure performed under general anaesthesia should be considered simple. We are glad that Dr Menon agrees with the interpretation of our study and appreciate his suggestions. Some thoughts were new to us and we certainly had not considered trial anaesthesia in patients with gastric cancer; we rely on other means of preoperative risk assessment.

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Barrett's Esophagus

H. W. Tilanus and S. E. A. Attwood (eds)
300 × 215 mm. Pp. 395. Illustrated 2002 Dordrecht: Kluwer Academic. £109-00

At first glance one is inclined to ask oneself: is it possible to write a book on this relatively uncommon clinical disorder? But on reading and exploring the work it is becoming more and more clear that Barrett's oesophagus is a real problem of growing importance. The incidence of adenocarcinoma of the distal oesophagus is increasing for reasons that are partly unknown, but one of the known causes is gastro-oesophageal reflux disease (GORD), which is considered to be the reason for the Barrett problem. This book deals not only with Barrett's oesophagus *per se*, but also with all aspects of reflux disease. The text is divided into six sections of between one and seven chapters, preceded by a chapter about the life of Norman Barrett himself. Anatomy, physiology, GORD, histopathology, molecular biological aspects, treatment of reflux disease, and adenocarcinoma and treatment modalities, are extensively decribed by many authors who are working in the field. The closing chapter deals with quality of life after oesophagectomy. One of the drawbacks of the multiauthor approach is some repetition throughout the book, but this is not excessively annoying as it permits room for differences of view about, for example, the surgical treatment of reflux disease. The framework of the book is simple, as are the illustrations. At least one colour picture of a Barrett's oesophagus would have been appropriate. Not all chapters end with a conclusion, but this is minor criticism. The most important quality of the book is the completeness and, as it gives a broad insight in the current ideas on Barrett's oesophagus, it may considered as a standard work. This book will appeal to gastro-intestinal surgeons and gastroenterologists.

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Pathology for Surgeons in Training: An A-Z Revision Text. 3rd ed.

D. L. Gardner and D. E. F. Tweedle
185 × 255 mm. Pp 404 Illustrated 2002 London Arnold £35 00.

As the authors state in their preface, this is not a book to be read, but to be dipped into. For a pathology textbook the variety of topics encompassed is wide: unexpectedly there are sections that deal with subjects as diverse as audit, radiology and telepathology. In addition there are useful sections on microbiology, hypothermia and genetics. Each topic takes no more than a few minutes to read and at the end of each section there is a box highlighting suggested further reading on associated subjects. This is in addition to cross-referencing within the text. At the end of the book there is an interesting, but by no means exhaustive, biography of eponymous surgeons and pathologists: a useful addendum for those 'who was so and so' questions. For a paperback book the quality of production is high. It is a convenient size, the paper is a good weight and quality, the typeface clear and the spine is sewn rather than glued (an important factor in durability). The figures are strikingly clear and certainly add to the text.

I have two minor criticisms. First, the card cover is single. After a couple of weeks of intermittent residence in my briefcase the corners have become bent and this is now affecting the pages. A flap cover of weightier board would complement the durability of the sewn binding. Second, there are one or two minor omissions in the index. Nevertheless, the authors have achieved their objectives in providing an easy to read and succint review of surgically oriented pathology. This book will be equally valuable for preparation of both candidates and examiners in post-graduate surgical examinations.

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Scientific Surgery

Oya M, Komatsu J, Takase Y, Nakamura T, Ishikawa H. Comparison of defecatory function after colonic J-pouch anastomosis and straight anastomosis for stapled low anterior resection: results of a prospective randomized trial. *Surg Today* 2002; **32:** 104–10.

Forty-two patients were followed for 1 year. Although rectal capacity was less after straight anastomosis, clinical function was similar in both groups.

Bogusevicius A, Maleckas A, Pundzius J, Skaudickas D. Prospective randomized trial of computer-aided diagnosis and contrast radiography in acute small bowel obstruction. *Eur J Surg* 2002; **168:** 78–83.

Eighty patients with no clinical evidence of intestinal strangulation were studied. There were no differences in accuracy between investigations, but computer-aided diagnosis was quicker (1 *versus* 16 h, $P < 0{\cdot}001$).

Ballotta E, Da Giau G, Baracchini C, Abbruzzese E, Saladini M, Meneghetti G. Early *versus* delayed carotid endarterectomy after a non-disabling ischemic stroke: a prospective randomized study. *Surgery* 2002; **131:** 287–93.

A total of 86 patients were randomized to early (within 30 days) or late (after 30 days) surgery. No strokes occurred in the waiting interval. There were no perioperative deaths and stroke rates were comparable (one in each group).

Singer AJ, Quinn JV, Clark RE, Hollander JE. Closure of lacerations and incisions with octylcyanoacrylate: a multicentre randomized controlled trial. *Surgery* 2002; **131:** 270–6.

The trial included 814 patients (924 incisions). Compared with conventional closure, gluing was quicker. After 1 week, there was no difference in infection or dehiscence rates. Appearances of the wounds at 3 months were similar.

Prandi M, Lionetto R, Bini A, Francioni G, Accarpio G, Anfossi A *et al.* Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy. *Ann Surg* 2002; **235:** 458–63.

Secondary analysis of two consecutive INTACC trials (3648 patients) revealed that both overall survival and relapse-free survival were related to the number of recovered lymph nodes in stage B, but not stage C, colonic cancer.

Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2002; **183:** 274–9.

Eleven trials including 2000 patients were analysed. Some 31 per cent responded to chemotherapy, but this reduced the rate of subsequent surgery, whilst increasing the rate of complete resection. Complication rates and survival were not affected.

McGrath C, Robb R, Lucas AJ, Stewart AHR, Underwood CL, Horridge JK *et al.* A randomized, double-blind, placebo-controlled study to determine the efficacy of immune modulation therapy in the treatment of patients suffering from peripheral arterial occlusive disease with intermittent claudication. *Eur J Vasc Endovasc Surg* 2002; **23:** 381–7.

Up to four injections of processed homologous blood increased claudication distance by over 50 per cent in 20 of 31 patients compared to 16 of 39 controls (65 *versus* 41 per cent, $P = 0{\cdot}06$). The difference reached significance in patients with short-distance claudication.

Bonazzi M, Gentile F, Biasi GM, Migliavacca S, Esposti D, Cipolla M *et al.* Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients. A randomized pilot trial. *Eur J Vasc Endovasc Surg* 2002; **23:** 445–51.

One hundred patients undergoing aortic aneurysm repair were randomly allocated to use of pulmonary artery catheter monitoring with optimal fluid administration or control groups. There were no deaths and no clinically significant differences in outcome.

Sui WT, Leong HT, Law BKB, Chau CH, Li ACN, Fung KH *et al.* Laparoscopic repair for perforated peptic ulcer. A randomized controlled trial. *Ann Surg* 2002; **235:** 313–19.

A total of 121 patients were included; nine patients in the laparoscopic group had conversion to open operation. Laparoscopic repair was quicker and reduced postoperative pain scores and requirement for parenteral analgesia. Death and complication rates, and duration of hospital stay, were similar (6 days for laparoscopic and 7 days for open surgery).

Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G *et al.* Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. *Eur J Surg Oncol* 2002; **28:** 418–23.

Some 358 patients were divided into high- and low-risk groups and then randomized to various follow-up regimens. Patients at high risk of recurrence who had adapted follow-up had significantly better 5-year survival rates than patients who had minimal follow-up.

The *BJS* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

British Association of Endocrine Surgeons abstracts

The following abstracts were presented at the British Association of Endocrine Surgeons meeting held in Pisa, Italy on 10th May 2002. The *BJS* prize was awarded to C. Wong, T. Lai, C. E. Stewart, J. M. P. Holly and the late J. R. Farndon for their presentation 'Selective oestrogen receptor modulators inhibit the effects of insulin-like growth factors in hyperparathyroidism'.

Total *versus* subtotal thyroidectomy in Graves' ophthalmopathy

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Background: Total thyroidectomy has often been suggested as the optimal surgical procedure in the control of Graves' ophthalmopathy but its value has never been scientifically proved. This is a preliminary report from a prospective, randomized study between total and subtotal thyroidectomy in patients with moderate to severe endocrine ophthalmopathy.

Methods: Forty-three women and one man with Graves' ophthalmopathy were included in a multicentre study; this report describes the first 25 after follow-up of 3 years. All patients had been treated preoperatively with thyreostatic drugs and had a clear ophthalmopathy at the time of surgery. Ten patients underwent subtotal thyroidectomy, after which 2·5 g of thyroid tissue was left, and 15 were treated with total thyroidectomy. All patients were followed up with clinical, biochemical and ophthalmological controls according to a standardized protocol at regular intervals up to 3 years after operation.

Results: The patients' opinions about their eye problems, as measured with a visual analogue scale, were similar before and during follow-up in the two groups. The ophthalmological scores for lid retraction, conjunctivitis, periorbital oedema, chemosis, proptosis and motility were similar in the two groups, both before and 3 years after surgery. There were four complications in the total thyroidectomy group (hypoparathyroidism, three; recurrent nerve palsy, one) and two after subtotal thyroidectomy (hypoparathyroidism, one; reoperation for bleeding, one).

Conclusion: From a 3-year perspective, total thyroidectomy and subtotal thyroidectomy seem to have similar effects on the outcome of endocrine ophthalmopathy in Graves' disease.

Evaluation of initial experience of day surgery for thyroid disease

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Background: Modern medicine is moving towards short-stay treatment models. The authors have recently opened a day-surgery unit (hospital stay 8–24 h) including thyroid surgery sessions. After 2 months of activity the results were evaluated in order to assess the adequacy of patient selection criteria and management protocols. The results of this initial experience are reported.

Methods: From October to December 2001 day surgery was offered to thyroid patients who fitted certain general admission criteria (clinical, logistical and social). Subjects with non-differentiated or locally advanced tumours, large or intrathoracic goitres and recurrent disease were excluded. Preoperative assessment was done on an outpatient basis, and included surgical and anaesthetic evaluation and preoperative examination. Patients were admitted on the day of operation and discharged 24 h later if they reached an adequate score on a modified Aldrite physiological scale. Otherwise they were transferred to a nearby surgical ward. Postoperative hypocalcaemia was treated according to a standard protocol. Postdischarge calcium control was prescribed as needed, and a dedicated telephone line was available 24 h a day for any urgent communication.

Results: In this interval 74 thyroid operations were performed (more than 30 per month) (59 women; mean(s.d.) age 41·3(11·9) (range 14–69) years). The preoperative diagnosis was single nodule ($n = 34$), multinodular goitre ($n = 24$) and differentiated thyroid cancer ($n = 16$, including five completion lobectomies). Thirty-nine thyroidectomies (33 open, six video), 34 lobectomies (26 open, eight video) and one isthmusectomy were performed. Among the 45 patients with no thyroid remnant mean(s.d.) postoperative calcium was 9·1(0·5) mg dl^{-1} on the day of surgery and 8·5(0·6) mg dl^{-1} on the first day after operation. Four patients experienced symptomatic hypocalcaemia and were treated according to a standard protocol, one of whom was the only patient transferred to the surgical ward. Asymptomatic hypocalcaemia was identified in seven patients, who were managed as outpatients. At follow-up all of them were highly satisfied with the treatment received.

Conclusion: A day-surgery unit can work safely and effectively with careful selection of candidates and reliable organization. A significant number of thyroid patients can be treated in this way, with relevant savings for the health system. Postoperative complications, particularly hypocalcaemia, can be safely and easily managed with standard protocols.

Gene therapy for goitre using fibroblast growth factor 2 receptor knockout

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Background: Levels of fibroblast growth factor (FGF) 2 and its receptor, FGFRI, are raised in thyroid hyperplasia, implicating these growth factors in goitrogenesis. It was hypothesized that FGF-2 is an essential cytokine for thyroid cell growth and goitre formation. FGF-2 is also an angiogenic factor and may play a role in angiogenesis associated with goitre formation.

Methods: A replication-defective adenovirus expressing dominant negative FGFRI (AdDN-FGFRI) was constructed to determine the role of FGF in human thyroid follicular cell growth and function *in vitro*. *In vivo* the potential antigoitrogenic action of targeted disruption of FGF-2 signalling in a mouse model of goitre was examined. This virus produces a kinase-deficient FGFRI which blocks signalling via the native FGFRI in infected cells. Controls included replication-defective adenovirus expressing only marker genes including 13-galactosidase or green fluorescent protein (GFP). Goitre was induced in mice by low-iodine diet, 0·075 per cent methylmethimazole in chow and 1 per cent perchlorate orally. In 14 days this regimen produced a doubling of thyroid weight (from 1·5 to 3·1 mg per thyroid lobe). 1×10^{10} particles of adenovirus were injected intravenously immediately before goitre induction. All mice were adult males in which there is quiescent angiogenesis. Blood vessels were identified by perfusion of rhodamine-labelled lectin specific for endothelial cells for 120 s 5 before sacrifice.

Results: *In vitro* treatment with exogenous FGF-2 inhibited human thyroid cell function and stimulated growth. Infection with AdDN-FGFR1 blocked these effects of FGF-2, confirming that the virus effectively inhibited FGF-2 actions. Specificity was confirmed using epidermal growth factor whose actions were not inhibited by AdDN-FGFRI. *In vivo* there was a significant increase in blood vessel density associated with goitrogenesis imaged by confocal microscopy. The goitre size of mice infected with AdDN-FGFRI was reduced by 66 per cent compared with that in control mice and GFP adenovirus-infected mice ($P < 0{\cdot}05$). This effect is predominantly via a direct effect on thyroid follicular cell growth.

Conclusion: AdDN-FGFRI effectively blocks FGF-stimulated thyroid cell growth. Specific knockout of goitrogenic cytokines offers a means of controlling goitrogenesis or treating established goitres in the future.

Video-assisted central neck lymph node dissection for papillary thyroid carcinoma

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Background: Video-assisted thyroidectomy (VAT) has been proposed for small papillary thyroid carcinoma (PTC). The authors have also attempted to remove enlarged central neck lymph nodes that were unexpectedly found during VAT for PTC by the video-assisted approach.

Methods: Twenty patients underwent VAT for PTC, six of whom underwent concomitant video-assisted lymph node dissection. The procedure was performed by a totally gasless video-assisted technique through a single 1·5–2·0-cm skin incision above the sternal notch. Dissection was performed under endoscopic vision using a technique very similar to conventional surgery. Only macroscopically enlarged lymph nodes were removed.

Results: There were six women with a mean(s.d.) age of 46·2(12·9) (range 35–70) years The mean(s.d.) number of removed lymph nodes was 2·3(1·2) (range 1–4). Lymph node dissection took about 15 min in all patients. Mean(s.d.) postoperative stay was 2·8(1·0) (range 2–5) days. Two transient postoperative hypocalcaemias were noted. No other complication occurred. Final histology showed lymph node metastases of PTC in one patient (two lymph nodes) and reactive changes in the others. Mean(s.d.) follow-up was 13·5(4·6) (range 6–18) months. Mean(s.d.) postoperative serum thyroglobulin was 1·6(2·1) (range 0–4·4) ng ml^{-1}. Postoperative ultrasonography showed no residual thyroid tissue nor evidence of recurrence in any patient. Mean(s.d.) uptake at postoperative iodine scintiscan was 2·7(2·2) (range 0–4·5) per cent. All patients considered the cosmetic result to be excellent.

Conclusion: Video-assisted removal of central compartment lymph nodes is feasible and safe. It may also be possible to perform complete central neck lymph node dissection. Some doubts still persist about the oncological validity of this approach and further larger and comparative studies are necessary.

Thyroid stunning with sodium ipodate

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Background: The use of iodine-rich oral contrast agents has been described as a way of rendering thyrotoxic patients euthyroid before operation. Despite promising results, this is still a new and experimental technique. The outcome of a series of 12 patients who were rapidly blocked using sodium ipodate (SI) preoperatively is reported. This technique has not been successful in only one patient, owing to poor compliance,

Methods: Twelve patients underwent total thyroidectomy for Graves' disease using SI blockade between November 1998 and December 2001. All were women. The age range was 24–73 (mean 39) years. Indications for SI use in place of conventional agents were: adverse drug reactions (eight), need to rapidly achieve euthyroid status (two), non-compliance (four) and failure to control with conventional drugs (two). SI dose, duration of treatment, preoperative thyroid function, intraoperative blood pressure, operative findings, operation times, estimated blood loss, mean hospital stay, complications and histopathology of excised specimens were recorded. These measurements were compared with those in 16 randomly selected patients who underwent total thyroidectomy for Graves' disease during the same period, using conventional blockade.

Results: Median duration of SI treatment was 11·5 days. Eight patients had mild transient hypocalcaemia after operation and one had prolonged hypocalcaemia. Histology revealed one occult papillary carcinoma. Mean operation time was 102 min. Mean maximum intraoperative systolic blood pressure was 127 mmHg and mean maximum diastolic blood pressure was 70 mmHg. Intraoperative blood loss in all 12 patients was minimal. Median postoperative hospital stay was 3 days. No patient experienced significant bleeding or recurrent laryngeal nerve injury. These results were comparable to those in control patients who had undergone conventional thyroid blockade.

Conclusion: SI blockade offers an effective alternative to conventional antithyroid drugs. It can be used to achieve rapid thyroid blockade before surgery both safely and effectively, when conventional blockade is not possible.

Management of cystic or predominantly cystic thyroid nodules

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Background: Conventional fine-needle aspiration biopsy (FNAB) has a high rate of inadequate specimens and false-negative results in cases of cystic or predominantly cystic thyroid nodules (CTNs). Ultrasonographically guided FNAB (UG-FNAB) allows direct sampling of the wall and/or the solid portion of CTNs, reducing the possibility of a geographical miss. The aim of this study was to verify the role of UG-FNAB in the management of CTN.

Methods: Between January 1998 and June 2001, 575 UG-FNABs of CTNs were performed. Thyroidectomy was carried out in 119 of these patients because of suspicious or malignant cytology, persistent non-diagnostic cytology, compressive symptoms and/or large nodule size or cyst recurrence after aspiration. The medical records of these patients were reviewed.

Results: The rate of non-diagnostic smears was 9·2 per cent. In patients with diagnostic smears the cytological diagnosis was benign lesion in 42, follicular lesion in 50, and suspicious or malignant lesion in 16. The final pathology revealed the CTN to be a benign nodule in 98 patients (82·4 per cent) and a carcinoma in the remaining 21 (17·6 per cent). In an additional 17 patients (14·3 per cent) an incidental microscopic papillary carcinoma, separate from the CTN, was identified. The overall accuracy of UG-FNAB was 88·0 per cent. No significant differences were found between patients with and without malignant CTNs with respect to age, sex, lesion size and echographic pattern (cystic or predominantly cystic lesion).

Conclusion: All CTNs should undergo FNAB because the rate of malignancy is significant and no clinical variable can reliably predict it. UG-FNAB may reduce the number of inappropriate smears. Recommendations for thyroidectomy should be based on UG-FNAB results, especially in small and asymptomatic CTNs.

Incision length for standard thyroidectomy and parathyroidectomy

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Background: There are many definitions of 'minimally invasive' thyroidectomy and parathyroidectomy in the

literature. No matter how they are defined, the main advantage is a shorter neck incision. Many 'minimally invasive' surgeons make an unfair comparison to the traditional Kocher incision of 8–10 cm. The aim of this study was to determine the current standard neck incision length for thyroidectomy and parathyroidectomy and to determine the variables that influence this length.

Methods: This was a retrospective study of the most recent 200 consecutive routine thyroidectomies and parathyroidectomies (excluding reoperation and neck dissection) carried out in a university hospital. The length of incision was routinely measured with a ruler before incision and was recorded in the operative note.

Results: Mean incision length for thyroidectomy ($P < 0{\cdot}001$) was: total thyroidectomy ($n = 73$), 5·5 cm; lobectomy ($n = 60$), 4·6 cm; multinodular goitre ($n = 49$), 5·8 cm; Graves' disease ($n = 8$), 5·5 cm; thyroid cancer ($n = 38$), 4·8 cm; benign ($n = 37$), 4·4 cm. The mean incision length for parathyroidectomy ($P < 0{\cdot}05$) was: bilateral exploration ($n = 28$), 4·1 cm; unilateral exploration ($n = 25$), 3·2 cm; focused exploration ($n = 14$), 2·8 cm. There was a positive correlation between the length of incision with thyroid volume/weight, age, body mass index (BMI) and duration of operation ($P < 0{\cdot}001$). For parathyroid, a positive correlation was found with extent of cervical exploration ($P < 0{\cdot}001$). Using multiple regression analysis, thyroid specimen weight and BMI in thyroidectomy, and extent of cervical exploration in parathyroidectomy, remained independent predictors of incision length.

Conclusion: Current neck incision length for standard thyroidectomy and parathyroidectomy is shorter than the traditional Kocher incision. The length of a thyroidectomy incision is determined mainly by the size of the thyroid gland and the BMI. The length of a parathyroidectomy incision is influenced by the extent of planned exploration.

Ultrasonographically guided wide-bore biopsy *versus* freehand fine-needle aspiration of the thyroid

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Background: Fine-needle aspiration (FNA) cytology is an obligatory investigation of the thyroid nodule. Its advantages include a near-zero false-positive and a low false-negative rate. In addition, the technique is safe, economical and repeat FNAs can easily be performed. However, up to 20 per cent of FNA samples are initially unsatisfactory largely owing to operator variability. In this unit thyroid FNAs are performed freehand with a small needle (21 or 23 G). Inaccessible nodules or previously inadequate FNAs are performed under ultrasonographic guidance by a designated radiologist with a larger-core biopsy gun (20 G). The ultrasonographically guided technique also enables sampling of the wall of a cyst under direct vision. In this study freehand FNA was compared with wide-bore guided core biopsy.

Methods: Some 262 FNAs and guided wide-bore thyroid biopsies performed over a 2-year interval (1 July 1999 to 30 June 2001) were included in the analysis. Clinical details, technician, aspiration cytology result and presence or absence of a cyst were all noted.

Results: Nineteen (15·7 per cent) of 121 ultrasonographically guided wide-bore biopsies were initially inadequate (AC0–1) as opposed to 66 (46·8 per cent) of 141 freehand FNAs. One of 21 ultrasonographically guided wide-bore biopsies recorded as cysts was malignant (AC5) whereas no cysts identified by freehand FNA were malignant. Of 34 patients with initially inadequate freehand FNAs or wide-bore biopsies, 11 had subsequent samples performed under ultrasonographic guidance following a freehand FNA. Of these 11 patients, ten had adequate samples (AC2–5). Fifteen of 34 patients had both initial and repeat samples performed by freehand FNA, of whom seven had adequate repeat samples. There were no complications as a result of the guided wide-bore biopsies.

Conclusion: Ultrasonographically guided wide-bore biopsy leads to more initial and repeat definitive diagnoses. The technique is safe despite use of a larger-bore needle. Ultrasonographically guided wide-bore biopsy is a useful tool for repeat thyroid sampling following an inadequate freehand FNA or as part of the assessment of multinodular goitre. When specific nodules can be targeted, ultrasonographically guided cyst aspiration can detect cystic carcinoma where freehand aspiration might not.

Pilot study of minimally invasive parathyroid surgery, with intraoperative parathyroid hormone measurement, as a day-case procedure

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Background: The aim of this pilot study was to assess the feasibility of unilateral, minimally invasive surgery (MIS), combined with intraoperative parathyroid hormone (PTH) measurement, in the surgical management of patients with primary hyperparathyroidism.

Methods: With local ethics committee approval, 22 consecutive patients (mean age 67 (range 42–85) years) with clear evidence of a parathyroid adenoma on sestamibi scan and neck ultrasonography were selected for study. Following informed consent these patients underwent a unilateral neck exploration performed through a 2·5-cm incision lateral to the sternomastoid. The retrothyroid space was explored by developing the plane between the sternomastoid and the lateral edge of the strap muscles. Blood samples for PTH measurement were taken at induction of anaesthesia, and before and after adenoma excision (+5 min, +10 min, +20 min). Patients were discharged within 23 h ($n = 10$) or on the day of surgery ($n = 12$) on calcium and vitamin D supplementation until outpatient review at 2 weeks.

Results: The adenoma was easily identified using this approach in all patients with a mean operating time of 29 (range 19–40) min. The plasma PTH concentration fell by more than 50 per cent of baseline levels at 5 min ($n = 18$), 10 min ($n = 3$) or 20 min ($n = 1$) after adenoma excision. None of the patients developed symptomatic hypocalcaemia during the 2 weeks after operation enabling cessation of oral supplements. Following this all patients were normocalcaemic (mean 2·35 (range 2·13–2·39) mmol l^{-1}). Histology confirmed a parathyroid adenoma ($n = 21$) or carcinoma ($n = 1$).

Conclusion: The results of this pilot study suggest that, following accurate preoperative localization of uniglandular disease, patients with primary hyperparathyroidism may be managed successfully and safely by MIS with intraoperative PTH measurement in the day-case unit.

Image-directed parathyroidectomy under local anaesthesia in the elderly

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Background: Surgical morbidity and mortality rates are increased in elderly patients. The purpose of this study was to evaluate the outcome of targeted parathyroid operations in patients aged over 70 years.

Methods: Thirty-six patients aged more than 70 years underwent targeted parathyroidectomy for primary hyperparathyroidism (HPT). Data were collected prospectively and reviewed retrospectively.

Results: There were 31 women and five men with a mean age of 78 (range 70–92) years. All 36 patients had symptoms attributable to HPT. All patients had successful preoperative localization with ultrasonography and/or sestamibi scintigraphy. Six patients had a history of previous neck surgery, including two with persistent/recurrent HPT. Thirty-two patients underwent neck exploration under local anaesthesia with intravenous sedation, but three required conversion to general anaesthesia. Intraoperative PTH monitoring was used in all cases. All patients were cured with no procedure-related morbidity. Postoperative data on symptoms were available for eight patients, and all reported an improvement.

Conclusion: A focused neck exploration under local anaesthesia provides a safe and efficacious alternative to bilateral neck exploration in elderly patients with successful preoperative localization of a solitary parathyroid adenoma. Parathyroidectomy improves symptoms and should be considered in most elderly patients with HPT.

Late results after unilateral surgery for hyperparathyroidism

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Background: Late outcome after unilateral parathyroidectomy for selected indications was assessed.

Methods: From October 1998 to March 2001, 454 patients with hyperparathyroidism (HPT) underwent operation. Concordant neck ultrasonography and ^{99m}Tc-radiolabelled MIBI scan was required to confirm the suitability of the unilateral approach. Parathyroid hormone (PTH) was measured intraoperatively. Serum levels of calcium and PTH in unilaterally operated patients were checked. Follow-up was 15·1 (range 6–30) months.

Results: Some 339 patients (75 per cent) could not be operated by a unilateral approach: 125 (28 per cent) had secondary HPT, 81 (18 per cent) had associated thyroid pathology requiring surgery, 48 (15 per cent) were excluded for obvious reasons (second operation, multiple endocrine neoplasia, previous cervical radiotherapy, etc.), and in 77 (17 per cent) preoperative imaging results did not allow a unilateral procedure. When preoperative MIBI scan or ultrasonography found more than one lesion, half of these were false-positive at surgery. Some 123 patients (37 per cent) with primary HPT were selected for a unilateral approach. Eight unilateral operations (7 per cent) were converted to a bilateral procedure. Three patients have already been reoperated for overlooked contralateral disease. Among 115 (35 per cent) of 329 patients with primary HPT who underwent unilateral operation, late postoperative calcium and PTH levels were available for 94; 86 (91 per cent) of the 94 had normal levels, six (6 per cent) had a high PTH level (half with vitamin D deficiency) and two (2 per cent) had a high calcium level, and are awaiting reoperation. The failure rate among selected cases was five (4 per cent) of 115.

Conclusion: Even with indications selected strictly by preoperative imaging and intraoperative PTH measurement, late results of unilateral surgery (96 per cent cure) barely match those of conventional bilateral surgery (98 per cent cured).

Late results of subtotal parathyroidectomy for hyperparathyroidism in multiple endocrine neoplasia type I

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Background: This was an assessment of late results after subtotal parathyroidectomy (PTX) for hyperparathyroidism (HPT) in multiple endocrine neoplasia (MEN) I.

Methods: Eighty-three (4 per cent) of 1888 patients operated for HPT had MEN I, of whom 79 were followed up. Sixty-six (84 per cent) underwent subtotal PTX, 55 of them (83 per cent) with bilateral thymectomy, and 13 (16 per cent) had resection of only grossly enlarged glands (1·1 per patient) because of the metachronous diagnosis of MEN I or referral pattern.

Results: First operation allowed resection of 3·2 enlarged glands per patient. Some 77 per cent of glands were hyperplastic (4 per cent intrathymic and supernumerary), 11 per cent were adenomatous and 12 per cent were histologically normal (half intrathymic and supernumerary). Mean(s.d.) postoperative calcium and parathyroid hormone (PTH) levels dropped from 11(2) mg dl^{-1} and 144(199) pg ml^{-1} to 9(9) mg dl^{-1} and 14(11) pg ml^{-1} respectively. Mean(s.d.) follow-up was 46(50) (range 18–360) months. Intraoperative PTH measurements (20 patients) were suggestive of cure in 18 and none of these patients was reoperated. Nine patients (11 per cent) had to be reoperated (three twice) after 78(53) months. Subtotal PTX yielded a lower reintervention rate than resection of grossly enlarged glands (five of 66, i.e. 8 *versus* 30 per cent; $P = 0·02$). Some 63 patients (80 per cent) were normocalcaemic, ten (13 per cent) were hypocalcaemic (two unsuccessful delayed autografts) and 7 per cent were hypercalcaemic (none after reoperation). The PTH level was normal, infranormal and supranormal in 80, 7 and 14 per cent of patients. After 1, 5 and 10 years, mean calcium and PTH levels were 9·4, 9·6 and 10·4 mg dl^{-1} and 57·3, 46·3 and 37·5 pg ml^{-1} respectively. By Kaplan–Meier analysis the rate of non-hypercalcaemic patients at 10 and 15 years was 60 and 51 per cent.

Conclusion: Subtotal PTX reduces the need for reoperation. Selective reoperation leads to long-lasting cure.

Risk factors for severe postoperative hypocalcaemia after surgical treatment of primary hyperparathyroidism

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Background: The number of patients referred for surgical treatment of primary hyperparathyroidism (pHPT) has quadrupled within 10 years in this clinic. With increasing volume, the expenses per patient bear increasing financial consequences for the hospital, requiring re-evaluation of treatment and the tradition of postoperative in-hospital surveillance. Postoperative hypocalcaemia is the only surgery-related reason for keeping the patient in hospital for more than 24 h after surgery. The objective was to identify well defined and prognostic risk factors, with a high sensitivity and an acceptable specificity for severe hypocalcaemia (serum ionized calcium less than 1·00 mmol l^{-1} (reference range 1·15–1·35 mmol l^{-1})), after surgery for pHPT, and to evaluate these risk factors prospectively.

Methods: This was a retrospective study comprising 340 consecutive patients, operated between 1991 and 1999, followed by a prospective study comprising 85 consecutive patients operated during 2000. The main outcome measure was the predictive value of identified risk factors.

Results: Incisional biopsy/excision of more than two parathyroid glands, thyroid surgery performed together with surgery for pHPT, preoperative serum levels of parathyroid hormone (PTH) greater than 25 pmol l^{-1} (reference range 1·1–6·9 pmol l^{-1}) and a history of previous neck surgery were identified as risk factors for severe postoperative hypocalcaemia in the retrospective study. In the prospective setting, the identified risk factors showed a sensitivity of 100 per cent (nine of nine) and a specificity of 25 per cent (nine of 36). The risk of severe hypocalcaemia after surgery for pHPT was zero (none of 50) in patients with none of the identified risk factors. The risk increased to 37 per cent (seven of 19) if the PTH concentration was more than 25 pmol l^{-1} and/or thyroid surgery was performed together with surgery for pHPT.

Conclusion: Patients with no risk factors for severe hypocalcaemia may be discharged early from hospital.

Special attention should be given to patients with one or more risk factors for severe hypocalcaemia.

Reoperation for persistent or recurrent primary hyperparathyroidism

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Background: The results of reoperations for persistent or recurrent primary hyperparathyroidism (HPT) were analysed.

Methods: From 1965 to 2000, 77 (4 per cent) of 1888 patients underwent reoperation for persistent HPT ($n = 54$) and recurrent HPT ($n = 23$) after a mean(s.d.) follow-up of 41(2) months (range 1 day to 190 months). Thirty-two patients (42 per cent) were referred from other units.

Results: There were 22 patients (29 per cent) with uniglandular lesions (UGL), 52 (69 per cent) with multiglandular lesions (MGL), two with carcinoma and one with parathyreomatosis. Fifteen patients (20 per cent) had familial HPT. Two patients underwent reoperation for unrecognized familial hypocalciuric hypercalcemia. Forty-nine (52 per cent) of the 94 resected abnormal glands were ectopic (seven extracervical). Some 29 per cent of adenomas were located in a fifth gland. Thirty-nine patients (51 per cent) had supernumerary glands that were pathological in 22 patients. The surgical approach in the 97 reoperations was cervicotomy (78 per cent); mediastinotomy, thoracotomy, thoracoscopy (16 per cent); and antebrachial graft resection. The sensitivity of sestamibi scan was 71 per cent and that of sestamibi scan combined with ultrasonography was 81 per cent (94 per cent in UGL, 78 per cent in MGL). Some 68 (88 per cent) of 77 patients were cured. No sporadic adenoma was missed. The seven uncured patients had MGL ($n = 5$, including four sporadic MGL), carcinoma ($n = 1$) and parathyreomatosis ($n = 1$).

Conclusion: Operative failures are due to MGL with supernumerary glands undetected by preoperative localization. Bilateral cervicotomy is recommended with exploration of the thymus and preoperative sestamibi scan to eliminate a hyperfunctioning mediastinal gland.

Five years' experience with video-assisted parathyroidectomy

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Background: A minimally invasive endoscopic approach to parathyroid glands was described in the literature more than 5 years ago but not many large series have been published. A 5-year experience of minimally invasive video-assisted parathyroidectomy (MIVAP) is described.

Methods: Between 1997 and 2002, 260 patients with primary hyperparathyroidism (PHPT) underwent MIVAP. They represented 71·4 per cent of a total of 364 cases referred to the Department of Surgery in the same period. Mean age was 55·7 (range 20–87) years. There were 55 men and 205 women. Fifteen patients also underwent an associated thyroid procedure (11 lobectomies and four total thyroidectomies). Mean operative time was 40·2 (range 10–180) min. Mean size of the adenoma was 1·8 cm in largest diameter. The conversion rate was 7·6 per cent (20 patients); the adenoma was not found at endoscopic exploration in nine of these patients, in six of whom it was found after conversion to open surgery. In the remaining three traditional exploration also failed to display the adenoma. Complications included two cases of laryngeal recurrent nerve palsy (0·8 per cent), transient hypoparathyroidism in six patients (2·3 per cent) and haemorrhage that required reoperation 6 h after parathyroidectomy in one patient.

Results: In five patients (1·9 per cent) a persistent PHPT appeared shortly after surgery. In two patients it was due to a false-negative intraoperative parathyroid hormone measurement and further exploration revealed a second adenoma missed during the first operation; the remaining three patients with persistent PHPT had undergone negative explorations (both endoscopic and open).

Conclusion: Minimally invasive surgery for PHPT can be performed safely in a large percentage of patients without an increased recurrence rate and with a similar rate of persistent disease. The follow-up is still too short to draw any definitive conclusion about the incidence of recurrent disease after MIVAP.

Role of parathyroid autotransplantation in surgical management of persistent/recurrent secondary hyperparathyroidism

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Background: It has been suggested that parathyroid autotransplantation (PA) after total parathyroidectomy (TP) facilitates the surgical management of persistent/recurrent secondary hyperparathyroidism (P/R-SHPT). The aim of this retrospective study was to compare the management of P/R-SHPT in patients previously treated either with or without PA.

Methods: Between 1988 and 2000, 32 patients underwent 52 reoperations (parathyroid hormone (PTH) more than 500 pg ml^{-1}) following an initial operation consisting of

TP + PA (group 1) ($n = 13$), subtotal parathyroidectomy ($n = 10$) (group 2), inadequate surgery ($n = 8$) (group 3), and TP ($n = 1$) (group 4).

Results: Group 1 underwent 32 localization studies, 16 graft and five neck explorations. Four supernumerary glands were identified. Twelve patients were cured (PTH less than 200 pg ml^{-1}) and one was lost to follow-up. Group 2 underwent 21 localization studies, 11 neck and one graft explorations. Eight patients were cured, one had persistent disease and one was lost to follow-up. Group 3 underwent 32 localization studies, 14 neck and four graft reoperations. Seven patients were cured and one had persistent P/R-SHPT. The patient in group 4 had three localization studies and was cured after one neck exploration. There were no recurrent laryngeal nerve injuries and no long-term hypoparathyroidism.

Conclusion: TP with PA did not simplify the subsequent surgical management of patients with P/R-SHPT.

Selective oestrogen receptor modulators inhibit the effects of insulin-like growth factors in hyperparathyroidism

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Background: Primary hyperparathyroidism (HPT) predominantly affects women and has a peak incidence at the perimenopausal period. This has led to speculation that an oestrogen imbalance may play a part in the pathogenesis of this condition. The authors have previously demonstrated the importance of the insulin-like growth factor (IGF) axis in HPT. The selective oestrogen receptor modulator (SERM) tamoxifen is the most commonly used adjuvant therapy in breast cancer and has been shown to modulate the IGF axis. The interactions of SERMs and IGF have been examined in a primary parathyroid cell culture model.

Methods: Estrogen (E2) receptors (alpha, beta) were evaluated by Western immunoligand blotting using radiolabelled tamoxifen. Sixteen parathyroid glands from 14 patients who underwent surgical treatment for HPT (primary, secondary/tertiary and confirmed on frozen section) were dispersed by enzyme digestion and cultured in 24-well plates. Following adhesion, the cells were transferred to serum-free (phenol red-free) media and dosed once with IGF (I or II) oestrogen SERMs (tamoxifen, faslodex (fasICI 182780)) for 96 h. Proliferation was assessed by measuring tritiated thymidine incorporation.

Results: Glands from patients with primary and secondary HPT express alpha and beta oestrogen receptors that bind tamoxifen. Parathyroid cells from patients with primary and secondary HPT had comparable responses and were therefore grouped together in the final analysis. Compared with control (100 per cent), IGFs (I and II) induced a significant increase in DNA synthesis (IGF-I mean(s.e.m.) 172(8) per cent, IGF-II 120(8) per cent; $P < 0{\cdot}05$). E2 at 10^{-8} and 10^{-4} mol l^{-1} (physiological range) inhibited DNA synthesis (10^{4} mol l^{-1} 74(9) per cent, $P < 0{\cdot}05$; 10^{4} mol l^{-1} 94(5) per cent, $P > 0{\cdot}05$) but had no significant effects on DNA synthesis with IGF (IGF-I 173(11) per cent, IGF-II 125(10) per cent; $P > 0{\cdot}05$). Tamoxifen 1 µmol l^{-1} inhibited basal DNA synthesis (77(3) per cent; $P < 0{\cdot}05$) and abolished the mitogenic activity of both IGF-I and -II (IGF-I 108(5) per cent, IGF-II 98(6) per cent; $P < 0{\cdot}05$). To clarify whether these effects can be ascribed to tamoxifens's E2 receptor antagonist property, faslodex (a pure oestrogen receptor antagonist) was examined under similar conditions. Faslodex at 10^{-11}–10^{-7} mol l^{-1} inhibited DNA synthesis in a dose-dependent manner (96(14)–60(11) per cent). Faslodex at 10^{-7} mol l^{-1} (pharmacological) inhibited both IGF-I and -II (IGF-I 79(15) per cent, IGF-II 61(13) per cent; $P < 0{\cdot}05$).

Conclusion: Tamoxifen and faslodex are both capable of reducing basal and IGF-stimulated DNA synthesis. There are obvious implications for cancer biology as well as therapeutic potential for SERMs in HPT.

Regional cerebral blood flow in patients with primary hyperparathyroidism measured by ^{99m}Tc-labelled ^{99m}Tchexamethylpropyleneamine-oxime single photon emission computed tomography

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Background: Single photon emission computed tomography (SPECT) is used to study cerebral blood flow (CBF) and cerebral metabolism in various neuropsychiatric disorders. Reduced regional CBF has been demonstrated in patients with severe depression and chronic fatigue syndrome. Such symptoms are also frequent in primary hyperparathyroidism. The aim of this study was to reveal possible changes in regional CBF in patients with primary hyperparathyroidism before and after operation.

Methods: Regional CBF was measured in 16 consecutive patients with primary hyperparathyroidism using SPECT with ^{99m}Tc-labelled HMPAO. All patients were women (median age 62 (range 33–78) years). The measurements were performed preoperatively and at 2, 4 and 12 months after parathyroidectomy. The MADRS depression scale was used as a parallel clinical test.

Results: Reduced regional CBF was found in 14 of 16 patients before operation. The mean(s.d.) preoperative regional CBF ratio was 0·87(0·11). At the 2-, 4- and 12-month timepoints, mean regional CBF ratios were 0·91(0·11), 0·95(0·10) and 0·94(0·11). Based on the variance component model, there was a significant time effect ($P = 0{\cdot}001$) when patient and location differences were controlled for. After operation improved regional CBF was seen in 13 patients, including one with presumed normal preoperative regional CBF. In six of eight patients with a preoperative MADRS score above 10 there was a parallel increase in regional CBF and fall in MADRS score.

Conclusion: The finding of preoperative reduced regional CBF followed by a significant increase in blood flow after parathyroidectomy might strengthen the indication for, and the timing, of surgical intervention.

BAES guidelines in the audit process

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Background: The British Association of Endocrine Surgeons (BAES) published their 'Guidelines for the Surgical Management of Endocrine Disease' together with a mission statement in November 2000. A study encompassing all the teaching and district general hospitals in one region has examined how closely clinical practice correlated with guidelines during the first year.

Methods: Questionnaires were sent out in December 2001 to all surgeons performing thyroid surgery in South-East Scotland. Data were collected for the full year 2001 and submitted centrally for analysis before a regional meeting attended by all the surgeons and an external contributor (Professor J. Farndon). Each unit had the opportunity to present its own data. Surgeons were asked if they were members of the BAES, if they had a copy of the guidelines, and how closely they adhered to key guideline recommendations.

Results: All 12 surgeons in the region participated. Three were from the two teaching hospitals within Edinburgh and they presented their data separately. In the six hospitals in the surrounding area, two had more than one surgeon who performed thyroid surgery (two and three respectively). The six surgeons who are members of the BAES and one other had copies of the guidelines. Some 196 thyroidectomies were performed in 2001 (between one and 67 per surgeon), 128 (65·3 per cent) in Edinburgh. Adherence to the guidelines is summarized in the table:

Key guideline recommendation	Adherence to guideline(%)
Preoperative calcium	78 (21–98)
Fine-needle aspiration	62 (16–82)
Isotope scan (not recommended)	18 (6–36)
Recurrent nerve visualization	91 (62–100)
Parathyroid visualization	86 (36–100)
Postoperative calcium	95 (50–100)

Values in parentheses are ranges

Conclusion: All thyroid surgeons in South-East Scotland are eager to improve their standard of practice. The first step in the audit process is for all surgeons to receive a copy of the BAES guidelines. An annual meeting will allow surgeons to compare their performance more easily with that of their colleagues and should stimulate closer adherence to the guidelines. To close the audit loop it is essential that outcome data are collected.

Randomized study of the effect of interferon-α on survival in patients with disseminated midgut carcinoid tumours

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Background: Midgut carcinoid tumours often present with widespread disease making curative surgery impossible. Medical treatment therefore plays a major role in the treatment of these patients.

Methods: In this randomized multicentre study the additional effect of interferon-α (IFN-α) on survival and risk of tumour progression in patients with midgut carcinoid tumours metastatic to the liver was evaluated. All patients ($n = 68$) had undergone uniform surgical treatment and hepatic arterial embolization of liver metastases before randomization. The patients were randomized to treatment either with octreotide alone ($n = 33$) or octreotide in combination with IFN-α ($n = 35$).

Results: Throughout the follow-up period (3–10 years) the total mortality rate was 41 of 68, equivalent to a 5-year survival of 46·5 per cent. There was no statistically significant difference in survival between the groups of patients treated with octreotide alone, or in combination with IFN-α. However, patients treated with IFN-α had a significantly reduced risk of tumour progression during follow-up ($P = 0{\cdot}008$).

Conclusion: The addition of IFN-α to octreotide after interventional treatment may retard tumour growth and may thus have a role in the treatment of patients with midgut carcinoid metastatic to the liver.

Regression of type II gastric carcinoids in patients with multiple endocrine neoplasia I and Zollinger–Ellison syndrome after surgical excision of all gastrinomas

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Background: Multiple gastric carcinoids occur in association with chronic atrophic gastritis and hypochlorhydria (type I) or in patients with multiple endocrine neoplasia (MEN) I combined with the Zollinger–Ellison syndrome (ZES) (type II). In both, hypergastrinaemia has been considered a common factor in pathogenesis, although an MEN I gene mutation has also been implicated in type II. If a patient with MEN I and ZES was rendered eugastrinaemic by a surgical procedure, the role of gastrin in carcinoid growth could be clarified.

Methods: Two patients with MEN I and ZES with multiple gastric carcinoids were identified and evaluated for a potentially curative procedure for their ZES. Both patients underwent distal pancreatectomy, enucleation of pancreatic head neuroendocrine tumours, and duodenotomy with excision of duodenal gastrinomas. Regional peripancreatic dissections were also performed. During follow-up of 5 and 6 years, serum gastrin levels, gastroscopic observations and biopsies were performed periodically.

Results: Both patients were rendered eugastrinaemic (serum gastrin less than than $100\ \mathrm{pg\ ml^{-1}}$) and have remained so. All tumours regressed completely during the first year in both patients. Annual gastroscopic examination revealed no evidence of any tumour during 5 years of follow-up.

Conclusion: Restoration of normal serum gastrin levels results in regression of multiple gastric carcinoids and gastrin is the critical factor in their pathogenesis (type II).

Functional characterization of adrenals from patients with primary aldosteronism

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Background: Conn's syndrome is characterized by autonomous production of aldosterone, suppressed renin activity, hypokalaemia and hypertension. The two major forms are unilateral adenoma and bilateral adrenal hyperplasia. In spite of thorough clinical investigation and careful histopathology it is often difficult to differentiate between adenoma and hyperplasia. The steroid synthesizing enzyme for aldosterone production is encoded by the gene *CYP11B2*, while the genes *CYP17* and *CYP11B1* are needed for cortisol production. The aim of this study was to achieve a functional characterization of adrenocortical nodules in primary aldosteronism by comparing clinical data, and endocrinological and histopathological evaluations with messenger RNA (mRNA) *in situ* hybridization of the genes encoding steroidogenic enzymes.

Methods: Four patients were selected from 16 subjected to adrenalectomy for adrenal disorders at Karolinska Hospital between 1987 and 1999. The inclusion criterion of this study was that small adrenocortical nodules had been detected that showed mRNA expression of the gene *CYP11B2*. Three patients had primary aldosteronism, and one had raised urinary cortisol and aldosterone concentrations. Computed tomography (CT) revealed adrenal masses in three patients. The fourth patient showed normal adrenals on CT, but venous sampling lateralized to one side. Four adrenals from patients operated for renal carcinoma were added as normal controls. Clinical data were collected, and endocrine and histopathological evaluation was performed. Resected adrenal specimens were paraffin embedded and analysed by an mRNA *in situ* hybridization technique using radioactive labelled oligonucleotide probes for the genes *CYP11B2*, *CYP11B1* and *CYP17*.

Results: Small adrenal nodules, not visualized on CT, showed expression of the *CYP11B2* gene. Adrenal masses seen on CT showed *CYP11B1* and *CYP17* gene expression. One patient was cured after operation and three patients still had raised aldosterone levels.

Conclusion: The four patients included in the study showed *CYP11B2* gene expression in nodules suggesting that these nodules are responsible for aldosterone production. They were not seen on CT. A combination of clinical data, histopathology, mRNA *in situ* hybridization of steroidogenic enzymes and outcome of adrenalectomy provided new possibilities for correct diagnosis of subsets of primary aldosteronism. This functional characterization should be included in the evaluation of primary aldosteronism.

Routine endoscopic ultrasonographic screening for asymptomatic pancreatic endocrine tumours in patients with multiple endocrine neoplasia I

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Background: Pancreatic endocrine tumours (PETs) are the single most common cause of death in patients with multiple endocrine neoplasia (MEN) I, primarily because of metastatic disease. Early identification, a key to improved prognosis of non-functional tumours, has been especially difficult in the past despite biochemical screening. The authors have found endoscopic ultrasonography (EUS) to be the most sensitive, specific, accurate and cost-effective localization procedure for detecting PETs in patients with sporadic and symptomatic MEN I, but it has not been used for screening.

Methods: EUS was used to evaluate all patients with known or suspected PETs referred to an endocrine surgical clinic. EUS was used in asymptomatic individuals with positive mutational analysis or family history and hypercalcaemia and/or evidence of a pituitary tumour. Patients with a history of previous pancreatic surgery at the time of referral were excluded.

Results: Some 132 EUS procedures were performed on 65 patients with MEN I from May 1994 to December 2001 to identify PETs. Of these, 13 completely asymptomatic patients met the criteria for this study. Six of the 13 had slightly raised gastrin levels (less than two times normal). EUS identified PETs in 11 of 13 patients, ranging in size from 0·4 to 4 cm. Ten of these patients subsequently underwent pancreatic or pancreatic and duodenal procedures to excise PETs. All had distal pancreatectomy in addition to duodenotomy (six) and enucleation of head tumours (five).

Conclusion: EUS is the most effective means of screening patients with asymptomatic MEN I who are at risk of PETs. These tumours can be detected before development of symptoms, or lymph node or liver metastases, and treated surgically with little morbidity.

Chromogranin A as a determinant of midgut carcinoid tumour volume

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Background: Neuroendocrine (NE) tumours are characterized by their capacity to synthesize, store and release hormonal products. These substances are stored in neurosecretory vesicles together with chromogranin A (CgA). The concentration of plasma CgA in patients with NE tumours is thought to reflect the degree of NE differentiation, total tumour burden and effect of medical treatment. The aim of this study was to analyse the correlation between tumour weight and plasma CgA levels as well as the influence of treatment with a long-acting somatostatin analogue (octreotide).

Methods: Nude mice bearing the transplantable human midgut carcinoid GOT1 were treated with the long-acting somatostatin analogue octreotide. Plasma CgA levels were determined using a competitive radioimmunoassay. The tumours were measured and weighed.

Results: There was a strong correlation between tumour weight and plasma CgA levels in untreated animals ($P < 0{\cdot}001$). In octreotide-treated mice, plasma CgA levels were significantly reduced compared with those in untreated animals; there was still a close correlation between plasma CgA and tumour weight ($P < 0{\cdot}001$).

Conclusion: This study demonstrates that plasma CgA levels are closely correlated to tumour burden, and that plasma CgA is well suited for monitoring the clinical course and outcome of treatment in patients with NE tumours.

Mini-adrenalectomy in comparison to open and laparoscopic approach

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Background: Laparoscopic adrenalectomy, the accepted gold standard, is still controversial for large tumours and malignancy. Outcome of mini-adrenalectomy (MA) using a subcostal incision of less than 15 cm was reviewed.

Methods: Fifty MAs (since July 1999) using an anterior transperitoneal approach in the lateral position were followed up prospectively. Thirty-two standard large-incision open adrenalectomies were reviewed retrospectively. The student *t* test was used to compare the difference in outcome. Published laparoscopic series were searched on Medline (PubMed) and compared with outcome of MA.

Results: The MA and open groups were comparable with respect to age (mean 49 *versus* 42 years), sex ratio and tumour size (median 4·5 *versus* 4·8 cm; range 1–12·5 *versus* 0·9–13 cm). There was no death. The median mini-incision size was 5 (range 4–15) cm. Complications in the MA group (12 per cent) included two splenectomies, two minor wound infections and postoperative pseudomembranous colitis. Patients in the open group had 15 complications (45 per cent) including splenectomies and respiratory complications. There was no significant difference in mean operating time (MA 117 min *versus* open 141 min). Patients who had MA discontinued intravenous analgesia earlier than those in the open group (median 2 *versus* 3 days; $P < 0{\cdot}001$), resumed a normal diet earlier (median 2 *versus* 5 days; $P < 0{\cdot}001$) and had a shorter postoperative stay (median 3 *versus* 9 days;

$P<0.001$). Outcomes following MA and laparoscopic adrenalectomy (morbidity 0–12 per cent, operating time 15–376 min, time to resumption of normal diet 1·3–1·7 days, hospital stay 2·2–11 days) were comparable.

Conclusion: MA was safe for all tumour types and sizes. This approach is superior to standard open adrenalectomy and comparable with laparoscopic adrenalectomy.

Variation in management of thyroid surgery between specialties in the Black Country, West Midlands

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Background: Thyroid surgery is performed primarily by general surgeons but otolaryngologists perform more than 15 per cent of all UK thyroid surgery. Current practice and variation in preoperative management strategies between the two specialties in the Black Country were studied.

Methods: All thyroid specimens received by histopathological departments at Royal Wolverhampton hospitals and Dudley group of hospitals over a 2-year period (1998–2000) were identified and a retrospective patient case-note analysis was undertaken. A total of 152 cases were identified; the case-notes were not traceable in four.

Results: Seventy-five procedures were performed by ear, nose and throat (ENT) surgeons and 73 by general surgeons. There was a total of 13 general surgeons (mean caseload 6 (range 1–16)) and five ENT surgeons (mean 15 (range 6–32) cases). Sex and age distribution was similar in the two groups as was case distribution (similar numbers of malignant tumours: ENT, four papillary and two follicular; general surgery, four papillary and three follicular). Thyroid goitre with a solitary nodule was the commonest presentation. Both groups had similar biochemical (more than 90 per cent had thyroid function tests) and preoperative evaluation. Some 60 per cent of ENT patients had ultrasonography of the thyroid gland compared with 45 per cent of patients in the general surgery group. However, the main difference between the groups was that 83 per cent of ENT patients with palpable thyroid masses underwent fine-needle aspiration cytology compared with 54 per cent in the general surgery group; the cytology results correlated similarly with histopathological reports in both groups. Sixty-six per cent of patients in the ENT group had preoperative assessment of the vocal cords compared with 22 per cent in the general surgery group. Complications were similar, with three patients complaining of hoarseness (no further assessment recorded), one reactionary and one secondary haemorrhage in the general surgery group, and two recurrent laryngeal nerve (RLN) neuropraxias and one reactionary haemorrhage in the ENT group. There were no recorded cases of permanent RLN paralysis or permanent hypoparathyroidism.

Conclusion: This study highlights the variation in management of thyroid surgery between specialties in the Black Country, West Midlands and emphasizes the need to follow published guidelines such as those set out by the British Association of Endocrine Surgeons, which are consistent with European standards. Increasing specialization of surgeons and closer cooperation between endocrine surgeons and otolaryngologists in multidisciplinary teams will improve both training and treatment outcomes.

Quantitative measurement of thyroglobulin messenger RNA in thyroid cancer

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Background: Serum thyroglobulin (Tg) measurement is essential in monitoring patients after thyroidectomy for thyroid cancer, but the results might be difficult to interpret in patients with anti-Tg antibodies. Tg messenger (mRNA) assay has been used to detect circulating tumour cells in blood, and early studies showed that Tg mRNA was more frequently positive in patients with metastasis than in patients with cured cancer. Such studies suggested that this technique would be more sensitive than Tg assay. However, later studies have produced controversial data, including positive results in control patients.

Methods: Tg mRNA was measured in 29 patients after total thyroidectomy for thyroid cancer and in 11 controls (four subjects without thyroid pathology and seven patients with benign thyroid pathology). The stage of the cancer was defined according to the findings of the latest whole-body ^{131}I scan performed under T4 withdrawal. Patients were classified as cured (negative scan, negative Tg; eight patients), with metastasis (positive scan in extrathyroid bed regions, positive Tg; eight patients), with thyroid remnants (positive scan in thyroid bed, positive Tg; eight patients) and discordant cases (negative scan, positive Tg; five patients). Tg mRNA was quantified in patients under T4 therapy who had a low level of thyroid-stimulating hormone. RNA was extracted from blood and analysed by quantitative reverse transcriptase–polymerase chain reaction with two sets of primers and internal probes specific for Tg mRNA. Glyceraldehyde-3-phosphate dehydrogenase mRNA amplification was used as an internal control. This method allowed the detection of Tg mRNA in thyroid biopsies.

Results: No correlation was found between Tg and Tg mRNA. Tg mRNA was undetectable in all patients with cured cancer and in all controls. Tg mRNA was present in one of eight patients with thyroid remnants and in one of five patients with discordant findings. Tg mRNA was not detected in any patient with metastasis.

Conclusion: These data do not support the usefulness of Tg mRNA measurement in blood in the monitoring of thyroid cancer.

Management of the neck in differentiated thyroid cancer

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Background: Locally metastatic differentiated thyroid cancer (DTC) has a predominantly good prognosis if adequately treated by surgery and postoperative radioiodine. Correct treatment of the neck improves local control and probably the mortality rate.

Methods: The outcomes of 81 consecutive patients who had a total thyroidectomy and level VI neck dissection for DTC were reviewed. All patients were treated by a single surgeon in a head and neck cancer centre over a 9-year period (1993–2002).

Results: Eighty-one patients with DTC, primarily investigated with fine-needle aspiration cytology and computed tomography/magnetic resonance imaging, had surgery planned using a risk stratification by gender, age, stage and histology. All patients had a total thyroidectomy and level VI lymph node dissection. Complications related to thyroidectomy included three cases of permanent hypoparathyroidism and three recurrent laryngeal nerve (RLN) palsies. A subset of 44 patients had a total of 53 lateral neck dissections for suspected lymph node disease (40 papillary and four follicular). The high incidence of nodal disease reflects the caseload referred to the regional thyroid service. Seventy-three per cent had selective neck dissections removing levels II, III, IV and V. Level V was only dissected above the accessory nerve if there was palpable disease in this area. Twenty-three per cent were modified radical (without level I dissection) and 2 per cent were radical neck dissections. The accessory was divided because of surrounding tumour in two patients. Complications of neck dissection included postoperative bleeding that required re-exploration (two), salivary leak (one), palsy of the long thoracic (one) and phrenic (one) nerves, and one death from pulmonary embolus. All but three patients were treated with ^{131}I after operation, and followed up with serial thyroglobulin measurements. There has been no local recurrence to date (follow-up 6–104 (mean 60) months).

Conclusion: Selective surgery in the neck can minimize morbidity and control local recurrence of metastatic DTC. Routine level VI lymph node dissection when performing total thyroidectomy for cancer does not increase rates of RLN palsy or hypoparathyroidism. Selective neck dissection provides good local control of nodal spread without sacrifice of neck structures in 75 per cent of patients.

Central neck dissection for sporadic micromedullary thyroid carcinoma

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Background: The treatment of medullary carcinoma (MTC) consists of total thyroidectomy and at least central neck node dissection (CND). Assay of serum calcitonin (CT) levels in patients with thyroid nodules allows early diagnosis of MTC. As there is a high morbidity rate associated with CND, the aim of this study was to evaluate its necessity in treatment of sporadic micro-MTC (size less than 1 cm).

Methods: This study was a retrospective multicentre review of 43 operated patients with micro-MTC from January 1991 to August 2001.

Results: Twenty-six women and 17 men with a mean age of 58 (range 28–87) years and no family history of multiple endocrine neoplasia were operated on. A diagnosis of sporadic micro-MTC was made by preoperative CT level in 29 patients, by frozen section in one and following definitive histology in 11 patients (eight with a preoperative basal CT level less than 10 pg ml^{-1} and three not tested). Two patients had clinically positive lymph nodes. Total thyroidectomy was performed in all cases with node 'picking' ($n = 7$) or CND ($n = 36$). Tumour size ranged from 0·2 to 9·0 (mean 4·1) mm. The tumours were solitary ($n = 32$) or multiple ($n = 11$). C-cell hyperplasia was found in 21 patients (six nodular type and 15 diffuse type) In the 41 patients with subclinical disease, 601 lymph nodes were analysed; none was involved by MTC. CT levels were undetectable in patients with subclinical disease at a mean follow-up of 32 months. Germline *RET* proto-oncogene screening was negative in 39 patients tested to date.

Conclusion: Since lymph node invasion is rare in sporadic micro-MTC, systematic CND is questionable.

Accuracy of fine-needle aspiration cytology in patients with thyroid nodules and a history of radiation exposure

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Background: Fine-needle aspiration (FNA) cytology is a useful method for selecting patients with thyroid nodules for thyroidectomy. Its value in patients who have been exposed to low-dose therapeutic radiation is questionable because these patients have an increased risk of multifocal benign and malignant tumours, and thyroid cancer is common.

Methods: From 1960 to 1999, 171 patients with one or more thyroid nodules who had a history of exposure to radiation were operated on; 49 of these patients had preoperative FNA. FNA results in these 49 patients were compared with those in an age- and gender-matched control group of patients with thyroid nodules who did not have a history of radiation exposure.

Results: Among the 49 patients with thyroid nodules and radiation exposure, six of 20 with a benign FNA cytology result had papillary thyroid cancer. None occurred in the dominant nodule that was aspirated. Six of 16 of the thyroid nodules that were suspicious by FNA were cancerous (two occult and four dominant), and all 13 nodules with positive FNA cytology were cancer. None of 14 control (non-irradiated) patients with a benign cytology result had cancer, whereas six of 15 with suspicious samples had thyroid cancer, and all 20 with a positive cytology result had cancer.

Conclusion: FNA cytology of thyroid nodules in patients with a history of radiation is not as accurate as that in non-irradiated patients, primarily because of coexisting occult thyroid cancers.

Long-term outcome of post-Chernobyl papillary thyroid carcinoma in children treated by surgery

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Background: The Chernobyl nuclear power plant accident happened on 26 April 1986. The most important outcome is a marked increase in the incidence of thyroid cancer in children and adolescents who lived within a 150-km radius of Chernobyl, the most heavily contaminated area, and who were born before and after the accident.

Methods: The long-term outcome of 22 children from Belarus (14 females and eight males; mean age at the time of diagnosis 9·6 (range 4–14) years) with radiation-induced papillary thyroid cancer, who received follow-up in Pisa, was analysed. The time from the accident to diagnosis of cancer was less than 2 years in one patient, 2–5 years in eight, and 6–9 years in 13. According to the tumour stage classification proposed by DeGroot and others, at the time of diagnosis eight patients had class 1 tumours (limited to the thyroid gland), six of whom were treated with lobectomy and two with total thyroidectomy from 1958 to 1993. Twelve children had class 2 (lymph node metastases) tumours, 11 of whom were treated with lobectomy and lymphadenectomy, and one with total thyroidectomy and lymphadenectomy from 1990 to 1993. Two children had class 3 tumour (extending beyond the thyroid gland) and were treated with lobectomy from 1992 to 1993. In the autumn of 1994 the children arrived in Pisa. In this same year seven patients with tumours initially diagnosed as class 1 underwent completion thyroidectomy, in four with associated lymphadenectomy; one was not treated. Eleven patients with class 2 tumours underwent completion thyroidectomy, two with associated lymphadenectomy, because of relapse, and one underwent lymphadenectomy only because of relapse. The two children with class 3 disease underwent completion thyroidectomy. The post-surgical treatment consisted in all cases of ^{131}I therapy for ablation of any thyroid residue and/or for the treatment of functioning local or distant metastases and L-throxine suppressive therapy.

Results: After a mean(s.d.) follow-up of 96(24) months, there were 11 patients with permanent hypoparathyroidism and two with vocal cord palsy. Of patients initially diagnosed with class 1 tumours, six were free from disease and two had lung metastases, one of whom also had lymph node and bone metastases. Of patients with class 2 disease, one was free from disease, four had lymph node relapse and seven had lung metastases, of whom five had associated lymph node relapse. One patient with class 3 disease at initial diagnosis was free of disease and the other had lymph node relapse.

Conclusion: Post-Chernobyl thyroid carcinoma in children is more aggressive than naturally occurring papillary thyroid carcinoma, and is associated with a high incidence of lung and lymph node metastases in all classes.

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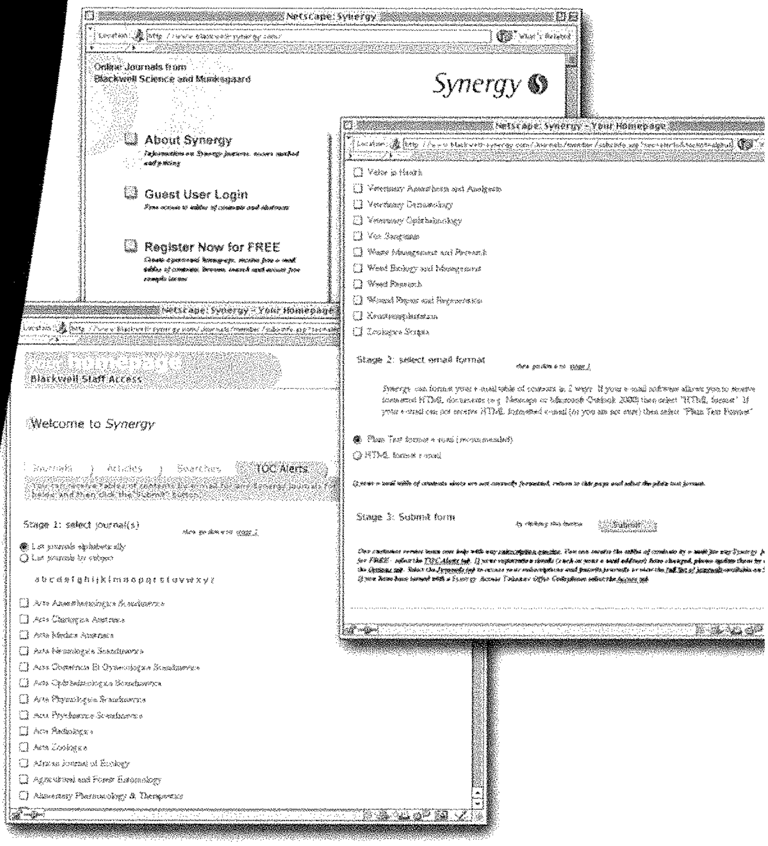
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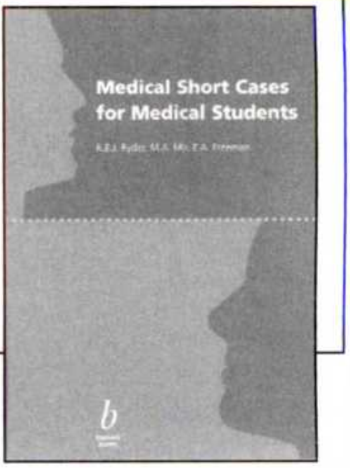
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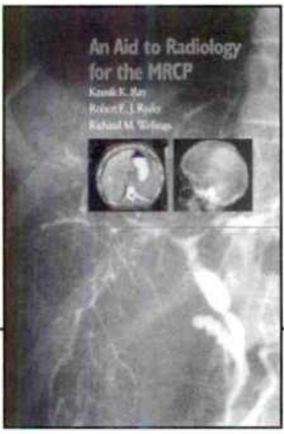
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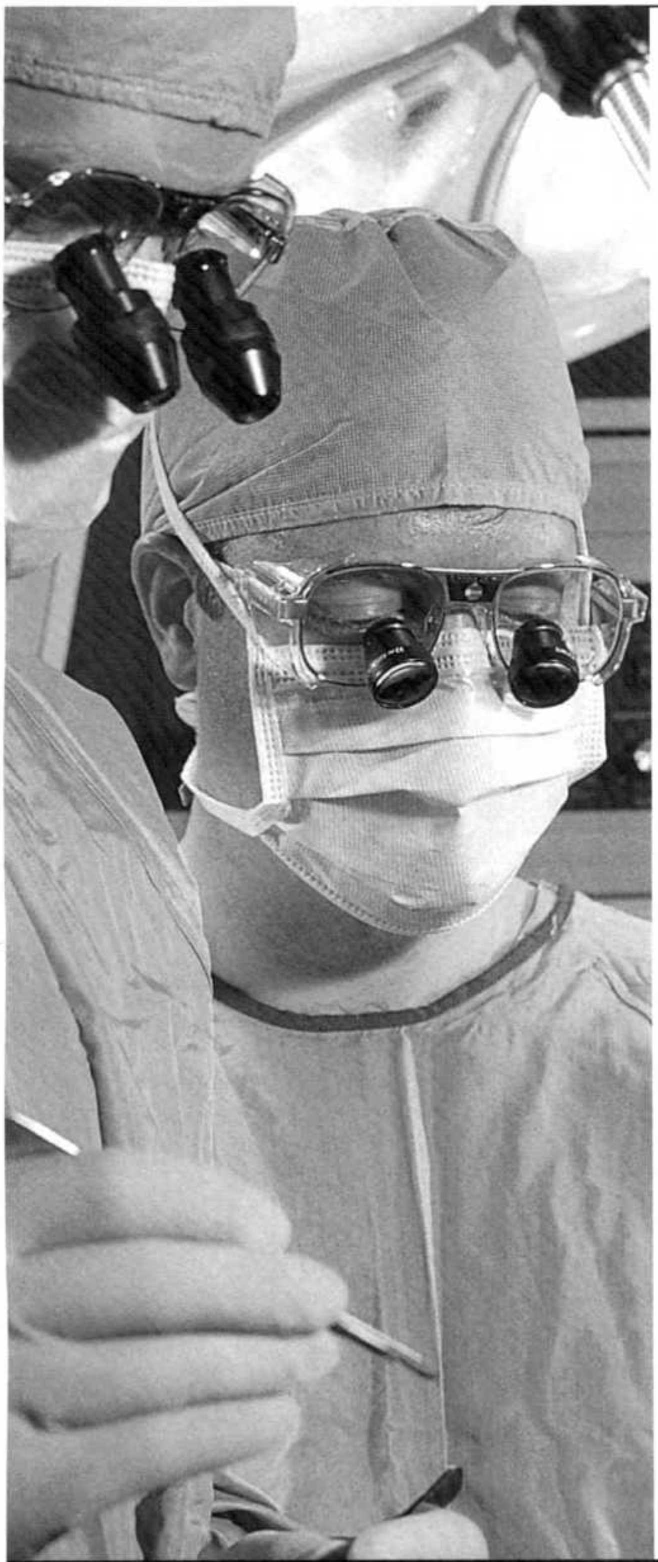

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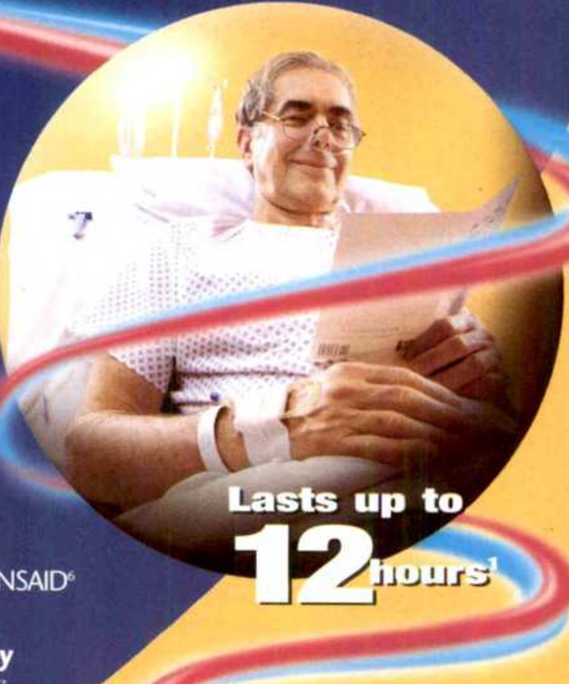

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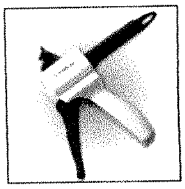

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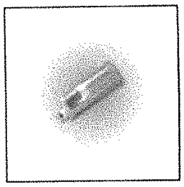

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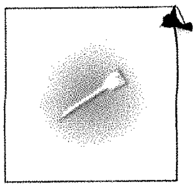

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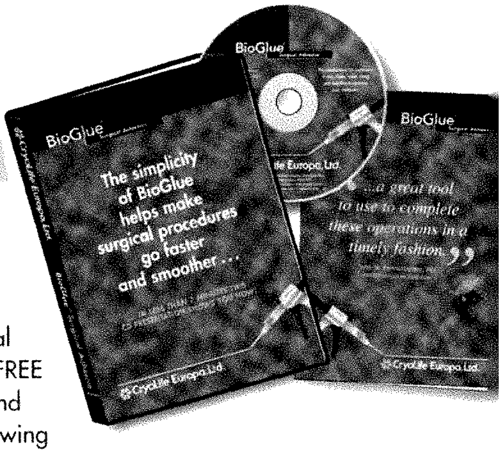
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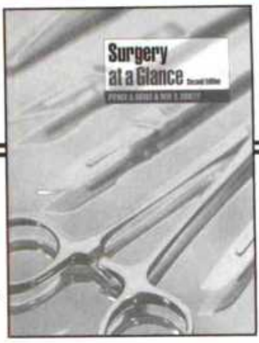

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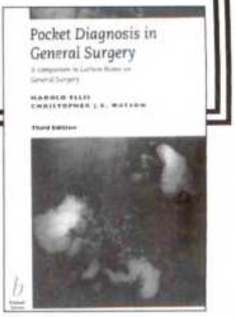

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Hepatocellular carcinoma and adjuvant intra-arterial [^{131}I]Lipiodol

B. Launois*† and G. Maddern†

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Hepatocellular carcinoma (HCC) is the most common cancer in men in Africa and Asia, with 20–150 cases for every 150 000 inhabitants. In western countries, the incidence is approximately four per 100 000 population, and the disease is thought to be responsible for up to 5500 deaths a year. HCC usually occurs within diseased liver following infection with hepatitis B or C (which are both increasing in incidence), alcoholic cirrhosis or haemochromatosis.

HCC is a major cause of death in patients with cirrhosis, and surgery remains the 'gold standard' of management. Two operations are available: transplantation and surgical resection. The risk of recurrence is high with both techniques[1,2], with the exception of cases where an incidental tumour is found at the time of transplantation. Long-term results following hepatectomy for HCC are unsatisfactory, with an 80 per cent recurrence rate at 3 years even with clear resection margins. Even when surgical resection is possible, the 5-year survival rate is usually less than 30 per cent[3]. To reduce the risk of recurrence, transplantation has been proposed for patients with tumours smaller than 3 cm in diameter and with fewer than three nodules[2]. Japanese authors have proposed using retinoids following a curative resection[4] but, unfortunately, this has proved toxic in humans. Since 1987, along with others, the authors have used [^{131}I]Lipiodol (May and Baker, Dagenham, UK) before both transplantation and tumour resection in an attempt to reduce postoperative tumour recurrence[5].

Lipiodol comprises iodized ethyl esters of fatty acids of poppy-seed oil; it contains 38 per cent iodine by weight, or 475 mg iodine per ml. When Lipiodol is injected into the hepatic artery, it tends to be concentrated and retained selectively in a HCC. The mechanisms of action are thought to include microvascular entrapment, uptake by the reticuloendothelial system, membrane adhesion of lipid droplets and/or cellular uptake. The standard iodine moiety of Lipiodol can be changed to radioactive ^{131}I by an atom for atom exchange reaction. [^{131}I]Lipiodol concentrates mainly in the liver, with a homogeneous distribution in normal liver and a heterogeneous distribution in cirrhotic liver. Its clearance from tumour is less than that from the non-tumorous liver. The biodistribution does not change in patients following a second or subsequent injection[6]. [^{131}I]Lipiodol treatment aims to deliver more than 120 Gy to the tumour, which is considered to be a tumoricidal dose, and such therapy has been found also to provide an analgesic effect and to help initiate the elimination of ascites[7]. A French multicentre prospective randomized study in 1997 showed that [^{131}I]Lipiodol therapy is associated with a better tolerance and fewer vascular complications than chemoembolization, although no survival advantage was demonstrated[8].

Preservation of hepatic vessels is an essential aim for patients about to undergo liver transplantation. With this in mind, radioactive Lipiodol can be used as a preoperative treatment and classified as neoadjuvant[5]. In the author's experience of 34 patients[9], 19 underwent resection and 15 had transplantation. Respective survival rates at 1, 2 and 3 years were 82, 70 and 61 per cent for the group as a whole, 79, 66 and 51 per cent for the resected group, and 86, 77 and 77 per cent for those undergoing transplantation. Transplanted patients who had preoperative [^{131}I]Lipiodol therapy had no tumour recurrence and a 5-year survival rate of 77 per cent[9].

Another option is to give [^{131}I]Lipiodol after operation[3]. In a prospective randomized study[10], 21 patients who received transcatheter hepatic intra-arterial injection of 1850 MBq [^{131}I]Lipiodol within 6 weeks of curative liver resection for HCC had a disease-free interval and a survival rate that were significantly better than those of a control group of 22 patients who received no adjuvant therapy. The 1- and 3-year overall survival rates for the [^{131}I]Lipiodol recipients and control group were respectively 91 and 85 per cent, and 86 and 46 per cent.

The significant worldwide incidence of HCC demands efficient and safe treatment options. The use of [^{131}I]Lipiodol has promise, but further randomized trials are required to determine the optimal regimen both before and after operation. The size of tumour that can be managed successfully by transplantation also requires reassessment in the setting of neoadjuvant [^{131}I]Lipiodol treatment.

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CHANGE OF PUBLISHER

From volume 90, issue 1, January 2003, the *British Journal of Surgery* will be published by John Wiley & Sons Ltd.

Therefore from **Monday 9 September 2002** all papers and correspondence should be sent to:

The Editor, *BJS*, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester
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Leading article

Adrenal incidentalomas

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Adrenal incidentalomas are tumours of the adrenal gland that are discovered incidentally when imaging studies are done for purposes other than searching for adrenal pathology. Incidentalomas are becoming more common as more computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography and other imaging studies are performed. Tumours found on scans that are directed to the adrenal gland to evaluate adrenal hormone hypersecretion or local symptoms, or to search for metastases, are not considered to be incidentalomas. Adrenal incidentalomas are found in 1–4 per cent of abdominal imaging studies depending on their sensitivity and resolution; most are non-functioning cortical adenomas that have minimal or no clinical consequences. Some incidentalomas, however, secrete hormones or are malignant, and their serendipitous discovery can lead to early diagnosis and treatment.

The challenge in the evaluation and management of these lesions is to balance the potential advantages of treating clinically significant disease early against the potential risks and cost of overtreating a clinically insignificant condition. The current controversies involving adrenal incidentalomas include (1) the extent of the initial investigation, (2) the significance of subclinical Cushing's syndrome, (3) the diagnostic certainty of malignancy, (4) the indications for and types of adrenalectomy, and (5) the need for, and the frequency of, biochemical or radiological monitoring if the tumour is not resected. A recent National Institutes of Health consensus conference on management of the clinically inapparent adrenal mass acknowledged the lack of prospective controlled studies to answer these questions definitively[1]. Below, I will summarize the evaluation and management recommendations from the perspective of an endocrine surgeon 'down in the trenches'.

Primary adrenal tumours

Tumours that present as adrenal incidentalomas include primary adrenal tumours, metastases from other primary cancers, and tumours of neighbouring tissues masquerading as adrenal tumours. Primary adrenal tumours may or may not secrete hormones and may or may not be malignant. In general, an adrenal tumour should be resected if it secretes hormones (e.g. phaeochromocytoma or cortical tumour that causes Cushing's syndrome or primary hyperaldosteronism), or if it is likely to be malignant. An incidentaloma need not be resected if it is non-functioning and likely to be benign.

Hormone-secreting primary adrenal tumours

The classical pathway for the diagnosis of hormone-secreting adrenal tumours follows the steps of (1) clinical suspicion of adrenal hormone hypersecretion, (2) confirmation of adrenal hormone hypersecretion by biochemical testing of blood or urine for the hormones or metabolites, and (3) imaging studies to locate the tumour(s). The evaluation of adrenal incidentalomas reverses these steps. The site is known, but the nature of the lesion is not. A thorough history and physical examination may lead to clinical suspicion, which can then be confirmed by biochemical testing. Hypertension is the most common clinical manifestation of adrenal tumours; the absence of hypertension makes aldosteronoma extremely unlikely, but does not exclude phaeochromocytoma or subclinical Cushing's syndrome. So, even in the absence of clinical suspicion, biochemical tests are still indicated for conditions such as phaeochromocytoma and Cushing's syndrome[2]. A recent series showed that 40 per cent of phaeochromocytomas are found initially as incidentalomas with only mild clinical manifestations. An adrenal cortical tumour that causes mild or subclinical Cushing's syndrome may be benign (adenoma) or malignant (carcinoma). Adrenal cortical carcinomas tend to be larger than adenomas and are more likely to secrete multiple hormones, including androgen and metabolites, in addition to cortisol. Patients with subclinical Cushing's syndrome are at risk of developing overt Cushing's syndrome and have multiple metabolic abnormalities that can be reversed by adrenalectomy[3]. Aldosteronomas tend to be smaller (less than 2 cm) and cause severe and poorly controlled hypertension early, so they are less likely to present as incidentalomas.

Adrenal cortical carcinomas

Adrenal cortical carcinomas can sometimes be difficult to distinguish from cortical adenomas histologically, in the absence of invasion or metastasis. The single best histological criterion for malignancy is an increased number of mitoses. For practical purposes, since hormone-secreting cortical tumours should be resected regardless of malignancy, the critical distinction is between non-secreting cortical adenomas and non-secreting cortical carcinomas. Since carcinomas tend statistically to be large and adenomas to be small, the size of a non-functioning adrenal tumour correlates with the risk of malignancy and is the best guide to determining the need for resection[2]. The size threshold for resection has been set as low as 2–3 cm and as high as 5–6 cm in different institutions. Although cortical cancers are most likely to be larger than 6 cm, increasing numbers of smaller (3 cm) adrenal cortical carcinomas are being reported. Older patients are more likely than younger patients to have non-secreting adenomas, and so it is appropriate to vary the resection threshold according to the age and co-morbidities of the patient. Tumours that have low attenuation (less than 10 Hounsfield units) on CT or take up NP 59 on scintigraphy are very likely to be cortical adenomas. Those that are heterogeneous or involve adjacent organs (invasion) are more likely to be cortical carcinomas.

It is controversial whether laparoscopic adrenalectomy is appropriate for adrenal cortical carcinoma. Patients with adrenal cortical carcinomas have a very high risk of local recurrence even after open adrenalectomy. Open adrenalectomy seems more prudent for tumours with obvious local invasion, and if lymphadenectomy or resection of adjacent organs is required. In any case, regardless of whether the adrenalectomy is performed conventially or laparoscopically, the adrenal gland must be resected completely, including peri-adrenal tissues, without breaching the tumour capsule[4].

Metastases to the adrenal gland

Metastases to the adrenal gland occur frequently in patients with disseminated cancer, but solitary metastases are less common. In such patients, the primary cancer is almost always known because of a previous diagnosis or a synchronous primary cancer elsewhere; solitary adrenal metastasis with occult primary cancer is extremely rare[5]. Although adrenal metastases are classically described as coming from melanoma and renal cell carcinoma, cancers of the lung, breast and colon are the usual primaries. In contrast to resection for cortical carcinoma, laparoscopic resection of solitary metastases to the adrenal is relatively safe, has a low risk of local recurrence, and can potentially be curative. The high mortality rate in these patients is due to disseminated cancer metastases that become apparent subsequently.

Other adrenal and non-adrenal tumours

Simple adrenal cysts or myelolipomas can be diagnosed definitively as benign by CT or MRI, and need not be resected unless they become large enough to cause local symptoms. The differential diagnosis of a non-functioning adrenal incidentaloma should also include tumours of the adjacent tissues and organs, such as the stomach (gastric stromal tumours), pancreas and retroperitoneum (lymphomas and sarcomas).

Recommendations for the evaluation and management of adrenal incidentalomas

1. Rule out adrenal metastasis. A routine history, physical examination and cancer screening tests, such as chest radiography, mammography and colonoscopy, will almost always make the diagnosis of a primary cancer should one exist. Laparoscopic adrenalectomy should be considered for a solitary metastasis.
2. Rule out hormone hypersecretion. A normal 24-h urinary collection for fractionated metanephrines and catecholamines rules out phaeochromocytoma. A normal low-dose dexamethasone suppression test or 24-h urinary cortisol rules out hypercortisolism (Cushing's syndrome). The plasma aldosterone level to renin activity ratio is indicated in hypertensive patients to diagnose aldosteronoma. All functioning adrenal tumours should be resected; most can be removed laparoscopically.
3. A large non-functioning adrenal tumour should be resected because of the risk of malignancy. I have a 3-cm threshold for young patients with no co-morbidity and a 5-cm threshold for older patients with significant co-morbidities. Large or obviously invasive tumours should have open resection. When an incidentaloma is not resected it should be monitored periodically for growth and hyperfunction, initially in 6 months and thereafter at longer intervals[6].
4. Needle biopsy is rarely indicated and can be dangerous. It rarely distinguishes adrenal cortical carcinoma from adrenal cortical adenoma and can cause tumour spillage, haemorrhage and phaeochromocytoma crisis. Fine-needle aspiration cytology may be useful when metastasis is the likely diagnosis and adrenal resection is not planned or when non-adrenal tumour, such as retroperitoneal lymphoma or sarcoma, is likely.
5. Even when the need for resection is obvious, hormonal studies to rule out phaeochromocytoma and sub-clinical Cushing's syndrome are still indicated. Perioperative endocrine preparation (α-adrenergic blockade to prevent phaeochromocytoma crisis or

steroid replacement to prevent addisonian crisis) is crucial in these patients.

6. Laparoscopic adrenalectomy is usually appropriate for known benign disease, and usually inappropriate for known invasive adrenal cortical carcinoma. It is also appropriate, in experienced centres, for phaeochromocytoma and solitary metastases[4].

Conclusion

The goal for the evaluation and management of adrenal incidentalomas is to resect hormone-secreting adrenal tumours and cancers without overtreating non-functioning cortical adenomas. Phaeochromocytoma, subclinical Cushing's syndrome and non-adrenal primary cancers should be routinely ruled out. When adrenalectomy is indicated, the laparoscopic approach is advocated except for obviously locally invasive cancer.

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Meta-analysis

Meta-analysis of techniques for closure of midline abdominal incisions

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Background: Various randomized studies have evaluated techniques of abdominal fascia closure but controversy remains, leaving surgeons uncertain about the optimal method of preventing incisional hernia.

Method: Medline and Embase databases were searched. All trials with a follow-up of at least 1 year that randomized patients with midline laparotomies to closure of the fascia by different suture techniques and/or suture materials were subjected to meta-analysis. Primary outcome was incisional hernia; secondary outcomes were wound dehiscence, wound infection, wound pain and suture sinus formation.

Results: Fifteen studies were identified with a total of 6566 patients. Closure by continuous rapidly absorbable suture was followed by significantly more incisional hernias than closure by continuous slowly absorbable suture ($P < 0{\cdot}009$) or non-absorbable suture ($P = 0{\cdot}001$). No difference in incisional hernia incidence was found between slowly absorbable and non-absorbable sutures ($P = 0{\cdot}75$), but more wound pain ($P < 0{\cdot}005$) and more suture sinuses ($P = 0{\cdot}02$) occurred after the use of non-absorbable suture. Similar outcomes were observed with continuous and interrupted sutures, but continuous sutures took less time to insert.

Conclusion: To reduce the incidence of incisional hernia without increasing wound pain or suture sinus frequency, slowly absorbable continuous sutures appear to be the optimal method of fascial closure.

Paper accepted 9 July 2002

British Journal of Surgery 2002, **89**, 1350–1356

Introduction

Incisional hernia is one of the commonest long-term complications of open abdominal surgery. In prospective studies, its incidence after midline laparotomy varies from 11 to 20 per cent[1–4]. Incisional hernia can cause pain and may lead to serious conditions, such as incarceration (6–15 per cent) or strangulation of bowel (2 per cent)[5,6]. Its repair is associated with recurrence rates of up to 45 per cent[7]. In terms of pathogenesis, numerous factors that may affect wound healing, such as diabetes mellitus, malignancy, wound infection, malnutrition, obesity, previous laparotomy, use of corticosteroids and surgical technique, are believed to play a role[1,3,8]. Of these, surgical technique is of special interest, as it is the only factor that is directly controllable by the surgeon.

Material and technique for fascial closure are often determined by local custom and surgical tradition. While a substantial number of randomized studies have been conducted to determine the ideal method, these have often been inconclusive or conflicting, and have left many surgeons uncertain about which method should be used. Two meta-analyses have recently attempted to determine which fascial closure method is best[9,10], but neither discriminated between rapidly and slowly absorbing sutures, comparing only absorbable and non-absorbable materials. As the characteristics of rapidly absorbable and slowly absorbable sutures differ substantially, discrimination between these groups seems warranted. Furthermore, the above meta-analyses included many studies with a follow-up of less than 1 year and a variety of abdominal incisions. For these reasons, the authors have conducted a new meta-analysis of the literature, including only midline incisions, with subdivision of suture material into rapidly, slowly and non-absorbing, and with a follow-up of at least 1 year. The aim of the study was to determine which method of fascial closure should be adopted to prevent incisional hernia and other complications.

Method

The Embase and Medline databases from 1966 to 2000 were searched by two independent reviewers, using the keywords 'randomised', 'randomized', 'abdominal', 'suture', 'technique' and 'material', with the boolean operator 'or'. The search was restricted to titles and abstracts. Criteria for inclusion of studies in this meta-analysis were prospective randomized controlled trials with at least 100 patients, comparing different suture materials and/or suture techniques for closure of a midline incision, with a follow-up of at least 1 year[11]. Trials of children younger than 15 years were excluded. Both independent reviewers extracted data and performed validation of inclusion criteria, discrepancies being resolved by discussion and consensus.

Twelve prospective randomized trials were excluded because they did not compare midline incisions or lacked sufficient follow-up[12–23]. Fifteen studies were included in the study and analysed[2,24–37]. In the analysis, suture material was categorized as rapidly, slowly and non-absorbing (*Table 1*)[38]. Suture technique was categorized as continuous or interrupted. Some studies varied both suture material and suture technique within a single trial[2,29–34]. In such circumstances, separate meta-analyses were performed within groups of trials that made the same comparison (e.g. interrupted rapidly absorbable *versus* continuous non-absorbable, interrupted rapidly absorbable *versus* continuous slowly absorbable); these are highlighted in the tables.

The primary outcome was postoperative incisional hernia. Secondary outcomes were wound dehiscence, wound infection, prolonged wound pain and suture sinus. Definitions of these outcome events were accepted as reported. 'Layered closure' was applied in only one study, and was defined as separate closure of the peritoneum and the musculoaponeurotic layer[37].

Analyses were conducted using Statistical Package for the Social Sciences (SPSS®, Chicago, Illinois, USA) and Egret® (version 2; Cytel Software Corporation, Cambridge, Massachusetts, USA) software. The Mantel–Haenszel method was used to summarize dichotomous outcomes of studies[39]. This method was used only if homogeneity of data was confirmed. Statistical homogeneity was assessed by χ^2 tests of heterogeneity. $P \leqslant 0{\cdot}05$ was considered to be statistically significant.

Table 1 Suture material and duration of total resorption[38]

Suture material	Total resorption (days)
Rapidly absorbable	
Catgut	15
Chromic catgut	90
Polyglycolic acid (Dexon®)	20
Polyglactin 910 (Vicryl®)	60–90
Slowly absorbable	
Polydioxanone (PDS®)	180
Polyglyconate (Maxon®)	180
Non-absorbable	
Nylon (Nurolon®)	No resorption
Polypropylene (Prolene®)	No resorption
Polyethylene (Ethibond®)	No resorption
Polyamide (Ethilon®)	No resorption

Dexon® (Davis and Geck, Wayne, New Jersey, USA), Vicryl® (Ethicon, Somerville, New Jersey, USA), PDS® (Ethicon), Maxon® (Davis and Geck), Nurolon® (Ethicon), Prolene® (Ethicon), Ethibond® (Ethicon), Ethilon® (Ethicon)

Results

Suture material

Several studies compared different suture materials inserted using a similar technique (either continuous or interrupted) (*Tables 2* and *3*)[2,24–28]. One study compared continuous rapidly absorbable suture material with continuous non-absorbable material in 751 patients[2]; significantly more incisional hernias occurred with rapidly absorbable sutures ($P = 0{\cdot}001$). It is interesting to note, however, that patients in whom non-absorbable material was used had significantly more suture sinuses ($P < 0{\cdot}001$) and prolonged wound pain ($P = 0{\cdot}003$). The same study also compared continuous rapidly absorbing sutures with continuous slowly absorbing sutures, and found a greater incisional hernia incidence after use of the former ($P < 0{\cdot}009$)[2]. Another study, however, comparing interrupted rapidly absorbing sutures with interrupted non-absorbing sutures, found no difference in respect of incisional hernia incidence[25].

Five studies compared slowly absorbing (polyglyconate (Maxon®; Davis and Geck, Gosport, UK) or polydioxanone (PDS®; Ethicon, Edinburgh, UK)) with non-absorbing (polypropylene (Prolene®; Ethicon or nylon)) continuous sutures in 2669 patients[2,24,26–28]. Meta-analysis of these studies did not identify any significant difference in incisional hernia incidence related to these materials ($P = 0{\cdot}75$). However, increased incidences of prolonged wound pain ($P < 0{\cdot}005$) and suture sinus ($P = 0{\cdot}02$) were noted after the use of non-absorbable, compared with slowly absorbable, sutures. No difference was found in respect of wound dehiscence or wound infection.

Suture technique

In six of the seven trials that compared continuous with interrupted suture technique, the suture material in the interrupted group was different from that in the continuous

Table 2 Randomized comparative studies

Reference	Year	No. of patients	Follow-up	Suture technique	Material*	Wound dehiscence (%)	Incisional hernia (%)	Wound infection (%)	Prolonged wound pain (%)	Suture sinus (%)	Conclusion on incidence of incisional hernia	Preference
Gys and Hubens[24]	1989	132	1 year†	Continuous layered	Nylon (N) 67	3·0	6·0	21			S = N	No preference
					Maxon® (S) 65	1·9	6·2	15·4				
Corman *et al.*[25]	1981	161	1 year†	Interrupted mass	Nylon (N) 49	0	8·9	4·1		12·2	F = N	Vicryl® (nylon and Prolene® more suture sinus)
					Prolene® (N) 53	1·9	4·4	9·4		5·7		
					Vicryl® (F) 59	0	0	10·2		0		
Israelsson and Jonsson[26]	1994	813	1 year†	Continuous mass	Nylon (N) 405	0·7	15·7	8·6	2·7		S = N	No preference
					PDS® (S) 408	0·5	15·1	9·4	2			
Carlson and Condon[27]	1995	225	2 years† 76%	Continuous mass	Nylon (N) 112	2·6	4	3·6	4·5	1	S = N	No preference
					Maxon® (S) 113	0	7	1·8	5·3	0		
Krukowski *et al.*[28]	1987	757	1 year	Continuous mass	PDS® (S) 374	0·3	3·5	3·2	3·2	0	S = N	PDS® (Prolene® more wound infection)
					Prolene® (N) 383	0·3	4·7	8	6·1	0·3		
Wissing *et al.*[2]	1987	1486	1 year† 78%	Interrupted	Vicryl® (F) 365	2·2	16·9	6·6	4·9	3	F > N	PDS® (nylon more suture sinus and wound pain)
				Continuous	Vicryl® (F) 379	1·6	20·6	9·0	8·6	1·4	F > S	
				Continuous	PDS® (S) 370	3·5	13·2	11·6	8·2	3·9	S = N	
				Continuous	Nylon (N) 372	2·1	10·3	7·2	16·7	7·7	Int F = Cont F Int F = Cont S	
Colombo *et al.*[29]	1997	614‡	3 years†	Interrupted 'Smead –Jones'	Dexon® (F) 306	0	10·4	1·6		0	Int F = Cont S	Continuous Maxon® (faster)
				Continuous	Maxon® (S) 308	0·3	14·7	1				
Brolin[30]	1996	229§	29 mo†	Continuous	PDS® (S) 120	0	10			0	Cont S < Int N	Continuous PDS® (faster)
				Interrupted figure of 8	Ethibond® (N) 109	1·9	18			5		
Trimbos *et al.*[31]	1992	340¶	1 year†	Interrupted	Vicryl® (F) 172	0	4	1	2	2	Int F = Cont S	Continuous Maxon® (faster)
				Continuous	Maxon® (S) 168	0·6	3	3	1	0		
Sahlin *et al.*[32]	1993	303	1 year†	Continuous	Maxon® (S) 148	2·7	13·5	10		0	Int F = Cont S	Continuous Maxon® faster)
				Interrupted 'far and near'	Vicryl® (F) 155	6·5	7·1	11		0		
Richards *et al.*[33]	1983	473**	1 year†	Interrupted 'far and near'	Dexon® (F) 244	0·9	0·5				Int F = Cont N	Continuous Prolene® (faster)
				Continuous mass	Prolene® (N) 229	2·0	2					
McNeil and Sugerman[34]	1986	105§	1 year†	Continuous	Dexon® (F) 54	0	10	4			Int N = Cont F	Continuous Dexon® (faster)
				Interrupted 'near–far–far–near'	Stainless steel (N) 51	2	9	2				

*Number of patients is given for each suture material. †Follow-up by means of physical examination. ‡Gynaecological cancer. §Morbidly obese. ¶Women only. **Only midline incisions included in present analysis. Incidence of incisional hernia was comparable (=), less (<) or more (>). F, rapidly absorbable; S, slowly absorbable; N, non-absorbable; int, interrupted suture technique; cont, continuous suture technique; mo, months. Dexon® (Davis and Geck, Wayne, New Jersey, USA), Vicryl® (Ethicon, Somerville, New Jersey, USA), PDS® (Ethicon), Maxon® (Davis and Geck), Nurolon® (Ethicon), Ethibond® (Ethicon), Prolene® (Ethicon)

Table 3 Analysis of suture material (same suture technique in both groups)

Suture type	No. of patients	Incisional hernia	Wound dehiscence	Wound infection	Suture sinus	Wound pain
Continuous rapidly absorbable *versus* non-absorbable[2]	379 *versus* 372	60 *versus* 31 ($P = 0\cdot001$)	6 *versus* 8 (n.s.)	34 *versus* 27 (n.s.)	4 *versus* 23 ($P < 0\cdot001$)	25 *versus* 50 ($P = 0\cdot003$)
Continuous slowly absorbable *versus* non-absorbable[2,24,26–28]	1330 *versus* 1339	119 *versus* 117 (n.s.)	17 *versus* 17 (n.s.)	106 *versus* 107 (n.s.)	12 *versus* 28 ($P = 0\cdot02$)	46 *versus* 85 ($P < 0\cdot005$)
Continuous rapidly absorbable *versus* slowly absorbable[2]	379 *versus* 370	60 *versus* 37 ($P < 0\cdot009$)	6 *versus* 13 (n.s.)	34 *versus* 43 (n.s.)	4 *versus* 11 (n.s.)	25 *versus* 23 (n.s.)
Interrupted rapidly absorbable *versus* non-absorbable[25]	59 *versus* 102	0 *versus* 6 (n.s.)	0 *versus* 1 (n.s.)	6 *versus* 7 (n.s.)	0 *versus* 9 ($P < 0\cdot05$)	—

n.s., Not significant. Mantel–Haenszel method

Table 4 Analysis of suture technique for different suture materials

Suture type	No. of patients	Incisional hernia	Wound dehiscence	Wound infection	Suture sinus	Wound pain
Interrupted *versus* continuous rapidly absorbable[2]	365 *versus* 379	48 *versus* 60 (n.s.)	8 *versus* 6 (n.s.)	24 *versus* 34 (n.s.)	3 *versus* 4 (n.s.)	14 *versus* 25 (n.s.)
Interrupted rapidly absorbable *versus* continuous non-absorbable[2,33]	609 *versus* 601	49 *versus* 35 (n.s.)	10 *versus* 13 (n.s.)	47 *versus* 37 (n.s.)	3 *versus* 23 ($P = 0\cdot001$)	14 *versus* 50 ($P < 0\cdot001$)
Interrupted rapidly absorbable *versus* continuous slowly absorbable[2,29,31,32]	998 *versus* 994	111 *versus* 94 (n.s.)	20 *versus* 23 (n.s.)	68 *versus* 87 (n.s.)	17 *versus* 25 (n.s.)	6 *versus* 11 (n.s.)
Interrupted non-absorbable *versus* continuous rapidly absorbable[34]	51 *versus* 54	5 *versus* 5 (n.s.)	1 *versus* 0 (n.s.)	1 *versus* 2 (n.s.)	—	—

n.s., Not significant. Mantel–Haenszel method

group[2,29–34]. This complicated any comparison between techniques. In most of these studies, no significant difference in incisional hernia incidence was found between continuous and interrupted sutures[29,31–34]. All studies favoured continuous suture, because the authors found that this method was easier and faster than using interrupted stitches and so saved operating time.

Separate analyses were performed for different suture materials (*Table 4*). None of these analyses identified a clear difference in incisional hernia incidence between interrupted and continuous suture methods. Combined analysis of all studies that compared continuous and interrupted sutures also failed to identify a difference in incisional hernia incidence (odds ratio 0·9 (95 per cent confidence interval 0·6 to 1·2); $P = 0\cdot40$). In addition, no differences were found in respect of incidence of wound dehiscence or wound infection. An increased incidence of both suture sinus and wound pain was noted after the use of continuous non-absorbable sutures compared with interrupted rapidly absorbable sutures ($P = 0\cdot001$ and $P < 0\cdot001$ respectively)[2,33].

In the process of searching for an ideal method, several technical variations on the interrupted or continuous techniques were developed. Of these, the interrupted 'figure of eight' technique, interrupted 'far and near' or 'near–far–far–near' technique, or interrupted 'Smead–Jones' technique did not reduce incisional hernia incidence compared with continuous sutures[29,30,32,33]. The continuous double-loop closure method also failed to reduce wound failure, although it could resist high intra-abdominal pressures[40]. When this method was compared with continuous running suture in a randomized trial, it was associated with significantly increased pulmonary complications (5 *versus* 17 per cent) and postoperative death (8 *versus* 21 per cent). For these reasons the trial was stopped early; it was not included in the present meta-analysis[40].

To determine whether using more suture material, expressed as an increased suture length : wound length ratio, might lead to a reduction in incisional hernia incidence, three studies measured suture length and compared this with wound length (*Table 5*). Two of these studies concluded that an increased suture length : wound length ratio of 4 : 1 or even 6 : 1 would decrease incisional hernia incidence significantly[35,36]. The third study did not find a decrease in incisional hernia incidence, although fewer wound dehiscences occurred after mass closure with an increased suture length : wound length ratio compared with layered closure[37].

Discussion

The ideal suture method should prevent incisional hernia and wound dehiscence, without increasing wound infection, wound pain or the formation of suture sinus. In the search for the best technique and ideal suture, meta-analysis can provide high-quality level I evidence. However, a valid meta-analysis requires very rigorous patient entry criteria, a series of high-quality trials, and qualitative and quantitative homogeneity for all groups that are compared in the analysis. Because many studies varied both suture material and suture technique within a single trial, one meta-analysis of all the data did not seem justified. Instead, the authors performed separate meta-analyses of groups of trials with comparisons of similar suture material and technique.

The type of incision has an important influence on the occurrence of incisional hernia. There is a lower incidence of incisional hernia after paramedian incision than after the more commonly used vertical midline incision[37]. For this reason, the present study included only trials that reported incisional hernia incidence after vertical midline incision; this contrasts with the recent meta-analyses of Weiland *et al.*[9] and Hodgson *et al.*[10], who included trials with a variety of incisions.

Another important factor is the duration of follow-up. Since incisional hernia may develop long after laparotomy, with up to 40 per cent occurring over 1 year after operation, adequate follow-up is essential[1,8]. Therefore, the authors included only studies with a follow-up (preferably by means of physical examination) of at least 1 year, in contrast to the previous meta-analyses which included a substantial number of studies (up to 54 per cent) with a mean follow-up of less than 1 year[9,10].

The ideal fascial closure should maintain tensile strength throughout the healing process. The dynamic process of wound healing can be divided into three phases[38,41]. The first exudative phase (days 1–4) is dominated by vascular, cellular and enzymatic processes, and does not provide any holding strength to the wound. It is followed by the proliferative phase (days 5–20), in which epithelialization, wound contraction and connective tissue repair take place[41]. During this phase, the tissue regains approximately 15–30 per cent of its original tensile strength. The process can be delayed by wound infection or inflammation. As most rapidly absorbable sutures lose most of their tensile strength within this phase (between 14 and 21 days), they are likely to increase the incidence of incisional hernia, especially if wound infection occurs[38]. This was confirmed by the study on 1486 patients, in which an increased incisional hernia incidence was found with the use of rapidly absorbable sutures compared with slowly absorbable or non-absorbable sutures[2]. Slowly absorbable and non-absorbable sutures retain their tensile strength up to the third phase (day 21 to several years), in which tissue is remodelled by the rearrangement and cross-linking of collagen fibres. During this phase, tissue regains up to 80 per cent of its original tensile strength[41].

Table 5 Suture length : wound length ratio in prospective studies

Reference	Year	No. of patients	Follow-up	Material	Suture technique	SL : WL ratio	Wound dehiscence (%)	Incisional hernia (%)	Wound infection (%)	Remarks	Conclusion on incidence of incisional hernia	Preference
Israelsson and Jonsson[35]	1993	363	1 year* 80%	PDS® or nylon	Continuous mass	> 4 < 4	0 0·7	9·0 23·7	4 4	SL : WL ratio similar for both materials	Less with ratio > 4	Ratio > 4
Varshney *et al.*[36]	1999	100	1 year* 85%	PDS®	Continuous mass	6·2 (6–7)		5	9			Ratio > 6
Kendall *et al.*[37]	1991	467	1 year* 78%	PDS® PDS® PDS® and catgut	Midline layered Midline mass Lateral paramedian layered	Mean 3·7 Mean 5 Mean 2·6	2·5 0 0	3·5 6·7 0	6 12 7	Less incisional hernia with paramedian than midline incision	Mass same as layered. No influence of SL : WL ratio	Lateral paramedian incision

*Follow-up by means of physical examination. SL, suture length; WL, wound length. PDS® (Ethicon, Somerville, New Jersey, USA)

In the present review, a discrimination was made between rapidly, slowly and non-absorbable sutures. No difference was detected in incisional hernia incidence between slowly absorbable and non-absorbable sutures[41]. Previous meta-analyses identified more incisional hernias after closure with absorbable sutures than with non-absorbable sutures[9,10], but Weiland *et al.*[9] did not discriminate between rapidly and slowly absorbable sutures. Hodgson *et al.*[10] performed a subgroup analysis of the slowly absorbable PDS. In agreement with the present meta-analysis, these authors found no difference in incisional hernia incidence between this material and non-absorbable sutures. Remarkably, they did not highlight this finding in their conclusion, stating simply that non-absorbable sutures should be used[10]. However, from the present analysis and other studies it is known that non-absorbable sutures are associated with an increased incidence of prolonged wound pain and suture sinus[2,23,25], and so slowly absorbable sutures should be used in preference.

As far as technique is concerned, all studies favoured continuous suture, a technique that has the benefit of being easier and faster than interrupted suture insertion, without increasing the incidence of herniation[29–34]. This is consistent with previous meta-analyses[9,10]. Of all alternative suture techniques tested, none was able to show a benefit[29,30,32,33,40]. The continuous double-loop closure method even increased the rate of pulmonary complications and postoperative death significantly[40], possibly because it decreased compliance of the abdominal wall, leading to an increase in intra-abdominal pressure which may promote abdominal compartment syndrome with its negative effects on pulmonary function[40]. This is an important finding because it stresses that the ideal closure method must not only provide adequate tensile strength, but must also provide adequate elasticity to accommodate any increase in abdominal pressure in the postoperative period.

One question that remains is how continuous suture should be inserted. Two studies stressed the importance of an adequate suture length : wound length ratio of at least 4 : 1[35,36], but this was not confirmed by a third study[37] in which no difference was found with an increase in suture length : wound length ratio of between 3·7 : 1 and 5 : 1. However, this third study contained several variables within its three study groups (mass/layered, suture length/wound length ratio, median/paramedian incision) and should be interpreted with caution. Regarding mass or layered closure, the meta-analysis of Weiland *et al.*[9] identified an increase in incisional hernia incidence and wound dehiscence after the latter. Mass closure is also easier and faster, and should be preferred. Thus, the ideal suture technique to reduce the incisional hernia rate appears to be mass closure using a continuous suture, with an adequate suture length : wound length ratio of at least 4 : 1. The suture material should be slowly absorbable.

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Review

Pathogenesis and clinical management of hereditary non-polyposis colorectal cancer

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Background: Hereditary non-polyposis colorectal cancer (HNPCC) is an inherited genetic condition associated with microsatellite instability; it accounts for around 5 per cent of all cases of colorectal cancer. This review examines recent data on management strategies for this condition.

Methods: A Medline-based literature search was performed using the keywords 'HNPCC' and 'microsatellite instability'. Additional original papers were obtained from citations in articles identified by the initial search.

Results and conclusion: The Amsterdam criteria identify patients in whom the presence of an inherited mutation should be investigated. Those with a mutation should be offered counselling and screening. The role of prophylactic surgery has been superseded by regular colonoscopy, which dramatically reduces the risk of colorectal cancer. Screening for extracolonic malignancy is also advocated, but the benefits are uncertain. Chemoprevention may be of value in lowering the incidence of bowel cancer in affected patients, but further studies are required.

Paper accepted 31 July 2002

British Journal of Surgery 2002, 89, 1357–1369

Introduction

The predisposition of some families to develop cancer at a young age was first recognized by Alfred Warthin in 1895 when his seamstress, from her family history, predicted her own death from cancer. Warthin studied this family extensively, calling it 'family G' in his publications[1–3], and found that gynaecological, colonic and stomach cancer occurred frequently. His work was largely forgotten until the early 1960s when the prevalence of cancer in families 'N' and 'M' was reported[4], leading to revived interest in family G and an updated review of its pedigree[5]. It was not until the 1980s that the idea of cancer family syndromes became fully accepted and the term Lynch syndrome was first used.

Lynch syndrome type I described families presenting with colonic cancers at an early age in the absence of multiple colonic adenomas. Lynch syndrome type II described similar families who also developed extracolonic cancers, particularly those of the female reproductive tract[6]. With the discovery that these syndromes were due to inherited defects in the genes that regulate the excision of errors occurring during DNA replication (mismatch repair genes), it became clear that the two Lynch syndromes were manifestations of the same disease. Both syndromes are now referred to as hereditary non-polyposis colorectal cancer (HNPCC) syndrome, a term that emphasizes the lack of extensive colonic polyposis in this condition. Colorectal cancer is the commonest cancer in those affected, and accounts for up to 5 per cent of all colonic cancers[7,8], although other extracolonic malignancies commonly occur.

The genetic basis

The principle behind inherited genetic risk is based on Knudson's 'two hit' hypothesis[9]. All somatic cells contain two copies (or alleles) of any gene, and Knudson suggested that both alleles must be disrupted or 'hit' before genetic function is lost. Patients with inherited risk are born with one defective copy of a gene, passed on from a parent affected with the disease (this is known as a germline mutation), and so require only a mutation in the normal allele before gene function is lost. The probability of a mutation within a single allele is greater than that of mutations in both alleles. This increases the likelihood of affected individuals developing a malignancy, usually at a younger age than in the 'normal' population. Cancers do not, in fact, arise from a single genetic defect but require an accumulation of mutations. In 1990 Fearon and

Vogelstein[10] published an elegant model to explain this process for colorectal cancer, suggesting that at least four or five mutations are necessary for malignancy to develop. This became known as the 'Vogelgram' and it provides the basis of our understanding of the evolution of cancer (*Fig. 1*); tumour suppressor genes such as adenomatous polyposis coli (*APC*), deleted in colorectal cancer (*DCC*) and *p53*, and oncogenes such as K-*ras*, are most commonly implicated.

In 1993 colorectal cancers from patients with HNPCC and sporadically occurring disease were noted to have a unique type of genetic abnormality, first known as replication errors and, subsequently, as microsatellite instability (MSI)[11–13]. Microsatellites are short segments of repetitive DNA bases that are scattered throughout the genome and found predominantly in intronic (non-coding) DNA[14]. MSI is defined as 'a change of any length due to either insertions or deletions of repeating units in a microsatellite within a tumour compared to normal tissue'[15] and results from failure of the cell to repair errors made during DNA replication. The enzyme DNA polymerase, responsible for DNA replication, is highly efficient but 'slippage' errors may still occur, particularly within microsatellites, leading to the insertion or deletion of nucleotide bases in the new DNA strand[16]. A group of intranuclear proteins, collectively known as the mismatch repair system, is responsible for removing these errors and maintaining the fidelity of the genome; failure allows errors to accumulate and MSI to develop. HNPCC is caused by germline mutations in the genes that code for mismatch repair proteins.

The mismatch repair system was first studied in bacteria in which three proteins, MutS, MutL and MutH, have been identified. At least seven mismatch repair genes are involved in human mismatch repair and their names are derived from their structural similarity to bacterial proteins: the MutS homologues (MSH), MSH2, MSH3 and MSH6; the MutL homologues (MLH), MLH1 and MLH3; and postmeiotic segregation (PMS) 1 and PMS2 (named before their true function was known)[17]. To date, no MutH homologue has been identified in humans. The mismatch repair proteins act in a complex manner (*Fig. 2*), with the MSH proteins being responsible for identifying abnormalities in the new DNA strand. MSH2 and MSH6 bind together forming a heteroduplex (the MutSα complex) that predominantly identifies single base mispairs, while MSH2 and MSH3 (the MutSβ complex) combine to identify short insertions or

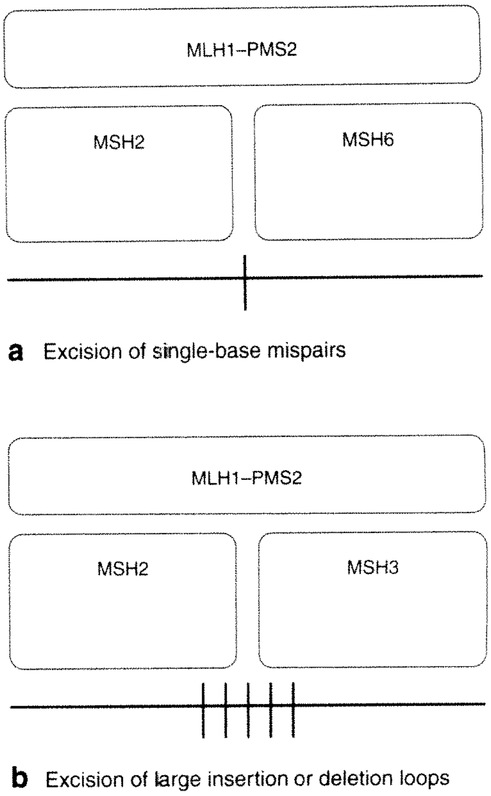
MLH1–PMS2
MSH2
MSH6
a Excision of single-base mispairs
MLH1–PMS2
MSH2
MSH3
b Excision of large insertion or deletion loops

Fig. 2 The mismatch repair system forms two complexes. **a** MutS homologue (MSH) 2 and MSH6 combine to form a heteroduplex (also called MutSα) that predominantly recognizes single nucleotide base mispairs, subsequently combining with the MutL homologue (MLH) 1–postmeiotic segregation (PMS) 2 heteroduplex to initiate DNA excision. **b** The MSH2–MSH3 heteroduplex predominantly recognizes larger DNA insertion or deletion loops (also called MutSβ), again combining with MLH1–PMS2 to initiate excision

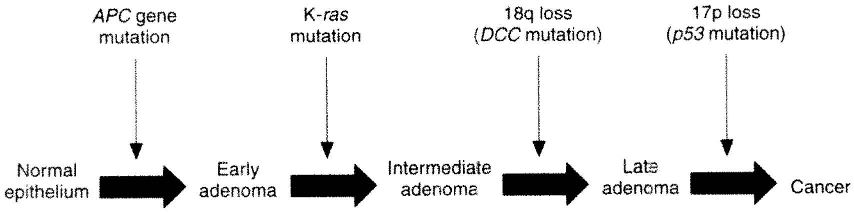

Fig. 1 Genetic mutations that occur in the progression from adenoma to carcinoma[10]

deletions[18]. MSH2 is essential for both complexes to function; mutations in this gene render the cell incapable of identifying any replication errors and extensive MSI develops. Functional overlap exists between MSH3 and MSH6, with cells deficient in either gene retaining some mismatch repair function and demonstrating a lower level of MSI compared with MSH2-deficient cells[19,20–22]. MLH1 and PMS2 also bind together to form a heteroduplex that interacts with the MutSα or MutSβ complex[23], stimulating excision and resynthesis of the abnormal DNA[24]. Both MLH1 and PMS2 are essential for mismatch repair, and mutations in either lead to the development of extensive MSI[23,25], similar to that which occurs when MSH2 function is lost[19,26]. The precise role of proteins such as MLH3 and PMS1 is not clearly understood. The most commonly mutated genes in HNPCC are MLH1 (33 per cent), MSH2 (31 per cent), PMS2 (4 per cent), PMS1 (2 per cent) and, rarely, MSH6[27,28]; a germline mutation in the transforming growth factor (TGF) β receptor type II gene has also been implicated[29].

Cancers demonstrating MSI appear to develop via an alternative genetic pathway to that described by Vogelgram, as aneuploidy and loss of heterozygosity are rarely encountered, and tumour suppressor genes are seldom mutated[30,31]. Instead, the function of genes with microsatellite regions incorporated into or close to their exonic coding regions (e.g. insulin-like growth factor II receptor (IGF-IIR), TGF-β receptor II (TGF-βRII), BAX protein and E2F4 cell cycle regulator[32–36]) are more commonly lost and cells tend to be diploid without loss of heterozygosity. In addition to the variation in the underlying genetic mutations of MSI-positive and MSI-negative cancers, differences in their histological appearances, colonic distribution and prognosis have led to the suggestion that they represent two separate clinical entities, arising through different genetic pathways[37].

To standardize the definition of MSI, the International Collaborative Group for HNPCC (ICG-HNPCC) recommends that at least five microsatellite loci (Bat25, Bat26, D2S123, D5S346 and D17S250) should be analysed for each cancer[15]. The degree of MSI should then be determined as high level (MSI-H) when instability is present in more than 30–40 per cent of the loci, as low level (MSI-L) when present in less than 30–40 per cent of the loci, and as stable (MSS) when no instability is detected[15]. Nearly all HNPCC cancers are MSI-H, although MSI-L occurs in HNPCC caused by MSH6 germline mutations[38]. MSI-L cancers are usually not caused by mismatch repair mutations[39] and are thought to be biologically similar to MSS cancers[15].

Presentation of hereditary non-polyposis colorectal cancer

Eighty per cent of patients at risk of HNPCC develop colorectal cancer during their lifetime at a mean age of onset that is lower than that in the general population of patients with bowel cancer[8,40,41]; they are also at risk of developing multiple cancers in a variety of organs (*Table 1*). Although the most common malignancy is colorectal cancer, one study has suggested that women at risk of HNPCC have a greater chance of developing endometrial cancer than of developing colorectal cancer[7]. The specific mismatch repair gene mutation may affect the disease phenotype. The incidence of colonic cancers is similar in patients with MLH1 and MSH2 mutations (84 and 71 per cent respectively), although those with MSH2 mutations show a higher incidence of extracolonic malignancy (48–61 per cent) than those with MLH1 mutations (11–42 per cent)[40,42]. Patients with MSH6 mutations are at greater risk of developing endometrial cancer (73 per cent) than patients with mutations in MLH1 (31 per cent) and MSH2 (29 per cent)[43]. Despite this, kindreds with identical mutations demonstrate a variety of phenotypes[44].

Pathological features of colorectal cancer in those at risk

HNPCC and sporadically occurring colorectal cancer have similar histological features and show a tendency to present in the right side of the colon, with approximately two-thirds of HNPCC being detected proximal to the splenic flexure[45,46]. They present at an earlier stage with a lower incidence of nodal disease (65 *versus* 35 per cent)[47] and distant metastasis[48]. Histologically, MSI-positive colorectal tumours are poorly differentiated, mucinous and likely to demonstrate signet ring cells[45]. There is often extensive lymphocytic infiltration with cytotoxic T cells[49,50], and

Table 1 Lifetime risk and age of onset for hereditary non-polyposis colorectal cancer-related malignancy[8,41]

Malignancy	Lifetime risk (%)	Median age of onset (years)
Colorectal	78	42
Endometrial	30–43	49
Gastric	19	54
Hepatobiliary	18	54
Urinary tract	10	60
Ovarian	9	47
Small bowel	1	49
Brain	1	Unclear

accumulation of both B and T cells around the tumour similar to that noted in Crohn's disease[51]. These distinctive histological features can identify cancers with MSI-H in 82 per cent of cases[52]. Jass[51] has subgrouped MSI-H cancers into: (1) proximally located, well circumscribed, well differentiated, mucinous carcinoma with limited lymphocyte infiltration; (2) proximally located, poorly differentiated carcinoma in which the epithelium is arranged in sheets or trabeculae; and (3) adenocarcinoma with a Crohn-like lymphoid reaction or tumour infiltrating lymphocytes.

Polyps in those at risk

The term hereditary non-polyposis colorectal cancer is misleading, because polyps are present in up to 30 per cent of affected patients[45,53,54]. The term does, however, indicate that extensive colonic polyposis is not an important feature. The polyps associated with HNPCC occur at a younger age and are larger in size than in the general bowel cancer population. Histologically, they tend to be villous adenomas with high-level dysplasia[45,55,56]. MSI-H is found in 67 per cent of polyps from HNPCC patients, and loss of expression of MLH1 or MSH2 genes is also common[57]. Colonoscopic screening has shown that one cancer is prevented for every 2·8 polypectomies performed in patients with HNPCC risk[58] and malignant transformation takes 2–3 years, compared with the general situation in which one cancer is prevented for every 41–119 polypectomies[59,60] and malignant transformation occurs after 8–10 years[56]. Polyps in patients with HNPCC risk seem to behave in an 'aggressive' manner[61] and progress to invasive cancer more rapidly than other adenomas[56,62].

HNPCC-associated polyps are found throughout the colon, which does not mirror the proximal distribution of cancer[57,63,64]. To account for this discrepancy, flat adenomas have been implicated in the evolution of HNPCC-related colorectal cancer; they are proximally distributed and constitute up to 51 per cent of polyps in these patients[65,66]. MSI can be found in 22 per cent of these polyps, as can a high incidence of TGF-βRII mutation[67]. The clinical significance of flat adenomas may have been underestimated because of the difficulty in detecting them at colonoscopy[68]. Interest has also focused on hyperplastic polyps and serrated adenomas. Although hyperplastic polyps are often disregarded, mutations in the K-*ras* and TGF-βRII genes have been reported[69], and MSI-H has been identified in 14 of 36 cancers in patients with hyperplastic polyposis syndromes[70]. Serrated adenomas have also been shown to demonstrate MSI-H and loss of expression of the MLH1 gene[71]. There is insufficient evidence to alter clinical practice, but large serrated or hyperplastic polyps found in the proximal colon of a patient with a family history of colorectal cancer are sinister and should be viewed with suspicion[70].

Identifying the risk of hereditary non-polyposis colorectal cancer

Patients with HNPCC risk must be identified so that they may be managed appropriately and their family members screened. As the incidence of HNPCC is low, screening the general population is inefficient[72] and resources should be directed at identifying families who appear to be at specific risk.

The Amsterdam criteria

In 1990 the ICG-HNPCC published guidelines known as the Amsterdam criteria to help identify those likely to be at risk of HNPCC[73]. In order to improve specificity, extracolonic cancers that occur in HNPCC were excluded. Because nearly 60 per cent of families with known germline mutations failed to meet the criteria[74], revised Amsterdam criteria (II) were issued in 1999 that included cancers of the endometrium, ureter, renal pelvis and small bowel (*Table 2*)[75]. Although gastric cancer is within the HNPCC risk spectrum, it is excluded to avoid overdiagnosis of HNPCC risk in the Far East where stomach cancer is prevalent. Atypical HNPCC families, such as that associated with MSH6 mutations when cancers occur later in life, may be missed[76,77] and may account for over 7 per cent of cases in which the family history does not meet the Amsterdam criteria[78].

The Amsterdam criteria rely heavily on family history; unfortunately, patients' recollections are not always accurate. Accuracy in reporting the site of the primary tumour and the age at diagnosis in first-degree relatives may be as high as 93–100 per cent, but this drops to 72–85 per cent for second-degree relatives[79]. The site of the tumour is often unknown; breast and colonic cancers are correctly identified in 72–85 per cent of cases, but only 30–60 per cent of endometrial or ovarian cancers are accurately recalled[80]. Some patients are unfamiliar with their family history. This is a particular problem for adopted children, those from separated families, or if the patient's father is not the person they believe him to be.

The Bethesda criteria

The Bethesda criteria have been developed to identify patients with MSI-positive colorectal cancers who might benefit from further analysis[81] (*Table 3*). Although over 90 per cent of HNPCC-associated cancers are MSI positive,

Table 2 The Amsterdam criteria

- Classical criteria (Amsterdam criteria I)[73]
  - There should be at least three relatives with colorectal cancer
  - One should be a first-degree relative of the other two
  - At least two successive generations should be affected
  - At least one colorectal cancer should be diagnosed before the age of 50 years
  - Familial adenomatous polyposis should be excluded in colorectal cancer cases
  - Tumours should be verified by pathological examination
- Revised criteria (Amsterdam criteria II)[75]
  - There should be at least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter or renal pelvis)
  - One should be a first-degree relative of the other two
  - At least two successive generations should be affected
  - At least one colorectal cancer should be diagnosed before the age of 50 years
  - Familial adenomatous polyposis should be excluded in the colorectal cancer cases
  - Tumours should be verified by pathological examination

HNPCC, hereditary non-polyposis colorectal cancer

Table 3 The Bethesda criteria[81]

Tumours should be tested for microsatellite instability in these situations:

- Individuals with cancer in families meeting the Amsterdam criteria
- Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or associated extracolonic cancer (endometrial, ovarian, hepatobiliary or gastric cancer, or small bowel adenocarcinoma, or transitional carcinoma of the renal pelvis or ureter)
- Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related cancer and/or a colorectal adenoma in which one of the cancers was diagnosed at age less than 45 years and the adenoma was diagnosed at age less than 40 years
- Individuals with colorectal cancer or endometrial cancer diagnosed at age less than 45 years
- Individuals with a right-sided colonic cancer with an undifferentiated pattern on histopathological examination diagnosed at age less than 45 years
- Individuals with signet ring cell-type cancer diagnosed at age less than 45 years
- Individuals with adenomas diagnosed at age less than 40 years

HNPCC, hereditary non-polyposis colorectal cancer

they account for less than 5 per cent of all colorectal cancers, while 15 per cent of sporadically occurring colorectal cancers also demonstrate MSI[82]. The finding of MSI should alert one to the possibility of HNPCC, but it does not necessarily equate with the diagnosis[81,83].

Evaluating patients at risk

Patients with a family history that fulfils the Amsterdam criteria should be investigated for an underlying germline mutation in the mismatch repair genes. Owing to the sensitivity of the genetic techniques employed and the absence of specific mutational hotspots associated with HNPCC identification, mutations may be recognized in only 70 per cent of families[27]. If a mutation is identified, screening of other family members is possible and those who are not found to be carriers can be reassured that their cancer risk is the same as that of the general public. Identified mutation carriers should be offered further counselling and cancer surveillance. For families with a history conforming to the Amsterdam criteria in which a germline mutation cannot be identified, all members should be regarded as mutation carriers and surveillance recommended. Specific groups in whom testing for HNPCC is particularly important are young patients with colorectal cancer and those with MSI-positive rectal cancer. Fifty-eight per cent of those under the age of 35 years demonstrate MSI, almost half being due to HNPCC[84], and two-thirds of MSI-H rectal cancers have germline mutations in the mismatch repair genes[85].

Other cancer family syndromes

Muir–Torre and Turcot's syndromes are two rare inherited syndromes linked to germline mutations in mismatch repair genes. Muir–Torre syndrome is characterized by the development of multiple sebaceous adenomas, carcinomas and keratoacanthomas, in association with at least one internal malignancy, often colorectal cancer[86], that usually demonstrate MSI-H. The family history of affected patients often fulfils the Amsterdam criteria[87,88], and germline mutations in *hMLH1* and *hMSH2*[89,90] have been identified. Turcot's syndrome includes colorectal and brain tumours exhibited as two distinct types, either as medulloblastomas with germline mutations in the *APC* gene and a familial adenomatous polyposis phenotype, or as gliomas with germline mutations in MLH1, MSH2 and PMS2 and an HNPCC phenotype[91–94].

Cancer surveillance and risk of hereditary non-polyposis colorectal cancer

Surveillance has been advocated for early detection of cancer in patients with HNPCC risk. The median age of onset of HNPCC and associated cancers is given in *Table 1* and although 5 per cent occur below the age of 30 years[73,95], malignancies may occur at any time and screening must be continued for life. Colonoscopy has proved to be effective screening for HNPCC-related colorectal cancer. A 15-year follow-up study examined the impact of regular colonoscopy in at-risk families. Those who underwent colonoscopy and polypectomy at intervals of 3 years had a 62 per cent reduction in the incidence of colorectal cancer compared with those who were not screened[96]. In patients with an identified germline mutation, the incidence of colorectal malignancy was 18 per cent in the screened group compared with 41 per cent in the control group. Although extracolonic malignancies in these groups occurred in 27 and 24 per cent respectively, there were nearly three times fewer deaths in patients undergoing surveillance ($P = 0{\cdot}003$). The optimal interval between colonoscopies remains uncertain. Cancers have developed within 42 months of a normal colonoscopy, leading to calls for a 1–2-yearly surveillance programme[97]. Colonoscopy can be distressing for patients and is not entirely free from risk, with haemorrhage or perforation reported in around 1 per cent of those undergoing a polypectomy[98–100]. Alternative imaging modalities such as computed tomographic colonography and virtual colonoscopy are possible options for the future.

The effectiveness of screening for endometrial and ovarian carcinoma is low[101–103]. Annual transvaginal ultrasonography and endometrial aspiration, commencing at age 25–35 years, are advocated by some[96,104], but the benefit of this approach has not been evaluated prospectively[105]. Screening for gastric and hepatobiliary cancer by regular gastroscopy, transabdominal ultrasonography of the biliary tree and liver function tests[106] has also been advocated, along with regular ultrasonographic examination of the urinary tract, cystoscopy and urine cytology for urinary tract malignancy[106,107]. There is little evidence to suggest that this level of screening confers any benefit and it should probably be reserved for families known to have a predilection to develop cancers at these sites. The Cancer Genetics Studies Consortium recommended screening only for colorectal and endometrial cancer in those with HNPCC risk[104], although the guidelines for screening as advocated by the ICG-HNPCC listed in *Table 4* are more intensive[106].

Surgical management

Some patients with HNPCC risk never develop malignancy, and several sites, such as the biliary and urinary systems, are not amenable to prophylactic excision. As colonoscopy significantly reduces the incidence of colorectal malignancy in those with HNPCC risk, prophylactic surgery is difficult to justify. Prophylactic colectomy may still have a role in patients with cancer phobia, those not compliant with screening, or those in whom colonoscopy is technically difficult[108,109]. In a survey of members of the National Society of Genetic Counsellors, only 17 per cent would accept prophylactic colectomy if known to be at risk of HNPCC, the rest preferring colonoscopy[110]. Of those at risk, 95 per cent opt for lifetime colonoscopic screening rather than prophylactic coloctomy[108].

While 94 per cent of women would accept lifetime surveillance for gynaecological malignancies, 50 per cent felt that after completion of their families they would consider the option of prophylactic hysterectomy or oophorectomy because of the unreliability of gynaecological screening[108]. Prophylactic surgery may have a role in the prevention of gynaecological malignancies for which screening is unreliable, but there is as yet no evidence that prophylactic hysterectomy and bilateral salpingo-oophorectomy confers benefit[41]. The optimal age for such an operation is probably about 35–40 years, but this has implications in terms of fertility and the need for long-term oestrogen replacement therapy[104]. A logical approach is to offer women with HNPCC-associated colorectal cancer who have completed their families the option of hysterectomy and bilateral salpingo-oophorectomy combined with colonic resection.

Patients with HNPCC-related colorectal cancer present a different problem and should undergo an extensive resection, because 45 per cent will develop a metachronous

Table 4 International Collaborative Group for Hereditary Non-Polyposis Colorectal Cancer guidelines for screening patients at risk

Site	Procedure	Lower age limit (years)	Interval (years)
Colon	Colonoscopy	20–25	2
Endometrium and ovaries	Gynaecological examination, transvaginal ultrasonography + CA-125	30–35	1–2
Stomach*	Gastroscopy	30–35	1–2
Urinary tract†	Ultrasonography and urine cytology	30–35	1–2

*Only if gastric cancer runs in the family. †Only if urinary tract cancer runs in the family cancer if treated by a standard segmental colonic resection[111]. Operative options include total colectomy with an ileorectal anastomosis or a proctocolectomy in which the rectum is removed, with or without a restorative procedure. After colectomy regular surveillance of the rectal stump is required because rectal cancer occurs in 6–12 per cent[112,113]. Patients with an MSH2 mutation are at higher risk of developing rectal cancer and knowledge of the genetic mutation might reasonably influence the surgical decision[106].

Chemoprevention

Chemoprevention is 'the inhibition or reversal of carcinogenesis through intervention with pharmacological agents before the development of clinical cancer'[114]. It could prove especially useful in those at risk from HNPCC, where it may be possible to reduce the chance of developing cancer in all susceptible tissues. Raised levels of cyclo-oxygenase (COX) isoform 2 have been identified in many colorectal cancer cells. Drugs that inhibit COX-2, such as aspirin and sulindac, reduce the incidence of polyps in patients with familial adenomatous polyposis and, although COX-2 is overexpressed less commonly in HNPCC than in sporadic colorectal cancer (67 *versus* 92 per cent)[115], aspirin and sulindac have been shown to reduce the MSI phenotype of colorectal cancer cell lines caused by mutations in the *hMLH1*, *hMSH2* and *hMSH6* genes[116]. Calcium supplements reduce the risk of developing colonic polyps[117], although the effect in HNPCC is unclear. Small reductions in the proliferation of colonic epithelium have been reported by some[118,119], but not by all[120]. The aim of the ongoing trial known as Concerted Action Polyp Prevention (CAPP II) is to evaluate the usefulness of dietary supplements and non-steroidal anti-inflammatory drugs in the prevention of colorectal polyps and should also provide valuable information regarding their role in HNPCC risk.

The oral contraceptive pill reduces the risk of endometrial and ovarian cancer in the general population and also decreases the incidence of ovarian cancer in carriers of the *BRCA1* or *BRCA2* mutations (genes that predispose to the development of breast and gynaecological cancer) by 60 per cent[72,121]. Its role in HNPCC risk has yet to be evaluated. The effects of chemoprophylaxis have far-reaching consequences in the management of HNPCC, but more work is required.

Prognosis in patients with hereditary non-polyposis colorectal cancer-related tumours

Crude survival data suggest that patients with HNPCC who develop bowel cancer have a better prognosis than those with sporadic disease[122,123]. A study from Finland confirmed an improved 5-year survival rate for both localized (85 *versus* 68 per cent) and advanced (40 *versus* 18 per cent) HNPCC-related cancers compared with the general cancer population[124]. Watson *et al.*[48] reported a significant improvement in 5- and 10-year survival rates for stage-matched HNPCC-related tumours compared with sporadic tumours, as well as a survival benefit in age-matched patients. Another study found no difference in survival for Dukes' stage A and B cancers but a significantly improved 5-year survival rate for patients with Dukes' C lesions (61 *versus* 21 per cent; $P < 0.01$) in HNPCC compared with the general cancer population[125]. However, two other studies have failed to identify any improvement for prognosis in HNPCC-related cancers[126,127].

As more than 90 per cent of HNPCC-related bowel cancers demonstrate MSI, studies investigating MSI-H colorectal cancer rather than HNPCC are of interest and have shown MSI to be an independent indicator of good prognosis[128–130]. Comparison of 5-year survival rates in patients under the age of 40 years with MSI positive and negative colorectal cancer has demonstrated a survival advantage (68 *versus* 32 per cent; $P < 0.05$) irrespective of tumour stage or grade[131], a finding confirmed by a similar study in patients under 50 years of age (76 *versus* 54 per cent; $P < 0.001$)[132]. The 5-year survival rate of patients with Dukes' C cancer who did not receive chemotherapy was 70 per cent in those with MSI-H lesions and 40 per cent in those with MSI-L or MSS disease ($P < 0.05$)[133]. Recent evidence suggests that Dukes' C MSI-H cancer has a better response to 5-fluorouracil chemotherapy; the 3-year survival rate for patients with MSI-H cancer was 90 per cent, compared with 43 per cent for those with non-MSI cancer in one study[134], and the survival rate at 54 months was 90 and 35 per cent respectively in another study[135].

Several theories have been put forward to explain the improved prognosis in MSI-H cancer. One suggestion is that loss of genes, such as *DCC*/18q, *p53*/17p and K-*ras*, confers a poor prognosis, because MSI-positive cancer seldom demonstrates loss of mutations in these genes, this accounts for the improvement in survival[136–141]. Another theory suggests that the accumulation of genetic abnormalities in MSI-positive cancer leads to the expression of aberrant proteins on the cell surface that are identified by the host's immune system triggering destruction of the tumour cells[142]. This corresponds with the observation that MSI-positive cancer often demonstrates a pronounced lymphocyte infiltration and a peritumour Crohn-like response, although it has been shown that MSI-positive cells fail to express β_2-microglobulin, a vital component in human leucocyte antigen (HLA) class I T cell-mediated cytotoxicity, suggesting that MSI-positive cells may, in fact, escape from immune-mediated destruction[143]. A third theory relates to failure of mismatch repair itself. As mutations are not excised and repaired during DNA replication, the mutational load within the cell increases with every cell division. This may result in a massive accumulation of mutations, rendering the cell incapable of performing the basic functions necessary for survival and leading directly to its death[144]. The idea that mismtach repair deficiency ultimately causes cellular destruction has led to the term 'effete malignancy' to describe MSI-positive cancer.

Moral issues

The diagnosis of HNPCC risk has psychological implications for patients and their families who are often young, fit and healthy. The best management strategy remains unclear; the usefulness of predictive genetic testing has been questioned as it may result in excessive emotional and psychological harm[145–147]. Discrimination by life insurance companies is a concern, and for this reason alone many patients refuse genetic testing[148,149]. Members of families at risk of HNPCC often overestimate the chance of inheriting the condition and have particular concerns about passing mutated genes to their offspring. This was cited as a reason for accepting genetic testing in 66 per cent of those seeking counselling[108]. Genetic testing is encouraged to alleviate unnecessary anxiety among those who do not carry a mutation and to enrol those with a mutation into a surveillance programme.

The ability to detect genes that predispose to cancer often precedes an understanding of the best long-term management for those affected, leading to uncertainty and anxiety for both doctor and patient. The American Society of Clinical Oncology believes that clinicians should assume an integral role in genetic counselling, provided they feel sufficiently well informed. Surgeons are often the first clinicians to encounter patients with hereditary cancer syndromes and so it is important that they have a clear evidence-based understanding of the implications and management of these conditions.

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Randomized study of the effectiveness of closing laparoscopic trocar wounds with octylcyanoacrylate, adhesive papertape or poliglecaprone

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Background: Several methods for skin closure are used, i.e. sutures, adhesive papertape and tissue adhesives. Little is known about the efficacy of these techniques in laparoscopic surgery. This study was performed to analyse the efficacy of octylcyanoacrylate, a new tissue adhesive, adhesive papertape and poliglecaprone for wound closure in laparoscopy.

Methods: From May 2000 to September 2001, 140 patients were included in a prospective randomized trial. Wounds were closed with octylcyanoacrylate ($n = 48$), adhesive papertape ($n = 42$) or poliglecaprone ($n = 50$). Closing time, wound infection, cosmetic results and costs were evaluated. A time–motion analysis was also performed.

Results: The patients in the three groups were well matched for age, gender and body mass index. Closing times per wound were 26, 33 and 65 s respectively for adhesive papertape, octylcyanoacrylate and poliglecaprone ($P < 0{\cdot}001$). Cosmetic results, as scored by the patients, were no different. The number of actions required to close each wound was 5·7, 8·3 and 21·0 for octylcyanoacrylate, adhesive papertape ($P = 0{\cdot}05$ *versus* octylcyanoacrylate) and poliglecaprone ($P < 0{\cdot}01$ *versus* octylcyanoacrylate and adhesive papertape) respectively. Octylcyanoacrylate was significantly more expensive than poliglecaprone and adhesive papertape.

Conclusion: Closure with adhesive papertape was the fastest method. The smallest number of actions required to close a wound was with octylcyanoacrylate. Adhesive papertape was the most cost-effective.

Presented to the European Association for Endoscopic Surgery Tenth International Congress, Lisbon, Portugal, June 2002

Paper accepted 28 June 2002

British Journal of Surgery 2002, **89**, 1370–1375

Introduction

There are several methods for wound closure. The most common procedure is closure with sutures, but adhesive papertape and tissue adhesives are newer alternatives. These last two methods are used especially for lacerations and low-tension wounds. Tissue adhesive and adhesive papertape are generally used in the emergency setting and have not been widely used in the operating theatre.

The use of adhesive papertape might have some advantages over suturing, including a lower infection rate, no risk of abscess development at the suture site (nowadays wounds are generally closed intracutaneously), a reduction in operating room time, good cosmetic results[1] and lower costs.

Recently, the octylcyanoacrylates, a new generation of tissue adhesives, were introduced. Butylcyanoacrylates are only effective in closing superficial lacerations with low tension. Octylcyanoacrylate (Dermabond®; Johnson & Johnson, Amersfoort, The Netherlands) has been designed to overcome the shortcomings of butylcyanoacrylates. Octylcyanoacrylate forms a stronger and more flexible bond; its breaking strength is three to four times higher than that of butylcyanoacrylates and is comparable to that of a 5/0 monofilament suture[2,3]. Advantages of tissue adhesives for incision and laceration wounds are the same as those of

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

adhesive papertape, and it might potentially be cost effective. Tissue adhesives also give an immediate wound sealing, providing a waterproof wound closure, which makes bandages unnecessary[2,4,5]. Furthermore, the risk of needle-stick injury, for the surgeon, is eliminated with the use of tissue adhesive or adhesive papertape.

Application of a tissue adhesive might be an attractive option for closure of laparoscopic trocar wounds, because of optimal apposition of the wound edges, simple and fast application, and limited after care. However, trocar wounds are deep stab wounds and the efficacy of tissue adhesives for these wounds has not yet been established in a randomized trial. Rosin *et al.*[6] showed in a prospective study that the infection rate was low, cosmetic results were excellent and patient satisfaction was high after closure of trocar incisions with octylcyanoacrylate.

The objective of the present study was to analyse the efficacy of wound closure with octylcyanoacrylate compared with that of adhesive papertape or suture closure. The results were also analysed in terms of incidence of wound infection, cosmetic results and cost-effectiveness.

Patients and methods

Patients eligible for a laparoscopic procedure were included in a prospective randomized two-centre trial. Inclusion criteria were patients scheduled for an elective laparoscopic procedure and age above 18 years. Exclusion criteria were previous laparotomy or pregnancy. All patients were randomized after giving informed consent. Patients were allocated to one of the three groups using a computer randomization.

Skin incisions were made with a knife and all were made in the skin lines. Trocars used for the surgical procedures were 5 and 10 mm in diameter. Wound closure was done according to a standard protocol. The fascia of the 10-mm trocar ports was closed with polydioxane (PDS®; Johnson & Johnson) or polyglactin (Vicryl®; Johnson & Johnson). One of three techniques was used for skin closure: (1) intracutaneous closure with poliglecaprone (Monocryl® 4/0; Johnson & Johnson) interrupted sutures, after which a dressing was applied for 24 h; (2) adhesive papertape strips (Steristrips®; Bioplasty/Uroplasty, Geleen, The Netherlands) 76 mm long and 6 mm wide were placed close to each other and were used to bring wound edges together; or (3) octylcyanoacrylate was applied once the wound edges had been apposed; no dressing was applied. Surgeons standardized the use of octylcyanoacrylate to minimize the variability of the level of technical expertise.

The primary outcome variable was time needed for closure of trocar wounds. The time needed to close a wound, including time needed for applying bandages, was measured either with a stopwatch or it was videotaped. The time was measured from when the surgeon was ready to start closure of the wound to when the wound had been closed. Operations in the Academic Medical Center were also subjected to a time–motion analysis (TMA)[7]. Closure of the trocar wounds was recorded on videotape for later analysis. The total number of actions needed per wound and number of action failures per wound were scored. Actions and failures for the TMA are defined in *Table 1*. Surgeons were allowed to convert to suturing after attempting the method chosen by randomization, if they were of the opinion that the test material was not going to give a desirable result. If, in case of octylcyanoacrylate or adhesive papertape, a change to poliglecaprone was made, all actions necessary to close the wound were counted as failures for the primary closing method.

Immediately after closure, the surgeon was asked to give his opinion on the time needed for wound closure and the practicality of the applied material. Both were multiple-choice questions; choices for time needed to close were:

Table 1 Definitions of actions and failures for time–motion analysis

	Octylcyanoacrylate	Poliglecaprone	Adhesive papertape
Action	Cleansing Squeeze ampoule Turn ampoule, soak tip Approximation of skin Fix with octylcyanoacrylate Rework octylcyanoacrylate Use of bandage	Cleansing Insert needle Pick up needle Pull needle through Tie knot Cut Use of bandage	Cleansing Taking adhesive papertape Approximation of skin Stick adhesive papertape to skin Use of bandage
Failure	Sticking of glove or instrument Wound opens Taking off octylcyanoacrylate Change to sutures	Deflection of needle Position needle again Wound opens Taking suture out	Adhesive papertape comes off Take away adhesive papertape Change to sutures

(1) far too long, (2) a little too long and (3) not too long. For practicality of the method, the choices were: (1) not practical, (2) not very practical and (3) very practical.

As secondary outcome variables, wound infection, cosmetic results and overall costs were analysed. Wound infection was defined as a wound with spontaneous drainage or requiring surgical drainage of purulent fluid. Patients were followed up at 10–14 days and 3 months after surgery. At follow-up, the incidence of wound infection and cosmesis were scored. Patients were asked to score their own cosmetic result. Surgical residents scored wound infections and cosmetic results; they were blinded to the method used for wound closure. Patients who had a diagnostic laparoscopy for malignancy were excluded from this part of the analysis, because laparotomy, if indicated, was scheduled within 6 weeks after the procedure. Patients were asked to fill out a validated cosmetic score on a visual analogue scale (VAS) for all incisions. Patients were also asked to complete the cosmetic scale of the Body Image Questionnaire (BIQ)[8]. Surgeons were asked to score the cosmetic result on a validated cosmetic VAS, one VAS score for all incisions. Incision scars were also scored according to the Holland Wound Evaluation Score (HWES)[9]. The percentages of optimal scores in the three groups were compared.

To analyse the overall costs per patient, the following costs were included: (1) costs of materials used, including those used as a result of failures and materials used for wound dressing and (2) costs for use of an operating room and medical personnel. Costs for materials used were: €13·90 for one ampoule of octylcyanoacrylate, €2·47 for one package of poliglecaprone, €1·15 per package of adhesive papertape and €0·42 per wound for wound dressing. Costs for the use of the operating room and medical personnel were €3·90 per min. Many patients were treated on a day-care basis. Extra costs for the treatment of wound infections were not accounted for.

Statistical analysis

From a pilot study it was calculated that 40 patients would be required in each group to find a statistically significant difference in the time needed to close the trocar incisions ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}8$).

Patient characteristics are presented as mean(s.e.m.). Means were compared by analysis of variance (ANOVA). Primary and secondary outcome variables are presented as median (range). To determine differences between the three groups in the primary outcome variable (time), non-parametric Kruskal–Wallis and Mann–Whitney *U* tests were used. For the secondary outcome variables ANOVA was used to determine the differences in the cosmesis questionnaire. Costs and TMA data were analysed with Kruskal–Wallis and Mann–Whitney tests. χ^2 test was used to analyse differences between the three groups in number of wound infections and in the HWES. The surgeon's opinion on time needed to close and practicality of the suture material is expressed as a percentage. Statistical analysis was performed using the statistical program Statistical Package for the Social Sciences 9·0 for Windows (SPSS, Chicago, Illinois, USA).

Results

Between May 2000 and September 2001, 140 patients were included in two hospitals. Patient characteristics are shown in *Table 2* and were not significantly different between the three groups. *Fig. 1* shows the trial profile.

The time needed to close trocar wounds, number of wound infections, cosmetic results and costs are shown in *Table 3*. Use of adhesive papertape was the fastest method of closing a trocar incision (26 s per wound and 80 s per patient), followed by octylcyanoacrylate (33 s per wound and 119 s per patient) and poliglecaprone (65 s per wound and 228 s per patient).

Table 2 Characteristics of patients randomized to octylcyanoacrylate, poliglecaprone or adhesive papertape

	Octylcyanoacrylate (*n* = 48)	Poliglecaprone (*n* = 50)	Adhesive papertape (*n* = 42)
Sex ratio (M : F)	26 : 22	23 : 27	23 : 19
Age (years)*	54(2)	52(2)	57(2)
Height (m)*	1·73(0·01)	1·72(0·02)	1·73(0·02)
Weight (kg)*	79(2)	75(2)	75(2)
Body mass index (kg/m²)*	26·4(0·7)	25·7(0·8)	25·0(0·6)
Laparoscopic procedure			
Cholecystectomy	29	27	14
Inguinal hernia	5	5	7
Diagnostic laparoscopy	14	18	20
Fundoplication	0	0	1

*Values are mean(s.e.m.)

Table 3 Wound closure times, cosmetic outcome and cost

	Octylcyanoacrylate ($n = 48$)	Poliglecaprone ($n = 50$)	Adhesive papertape ($n = 42$)	P
Time needed to close per wound (s)*	33 (7–140)	65 (22–224)	26 (7–143)	< 0·001†¶**
Time needed to close per patient (s)*	119 (22–420)	228 (65–894)	80 (20–571)	< 0·05§, < 0·001¶**
Wound infection	5	3	2	n.s.
Cosmetic result				
Patients' opinion				
Cosmetic scale BIQ (3–24)	19·0	19·4	19·1	n.s.
Cosmetic VAS*	7·7 (1·1–10)	8·2 (3·8–10)	8·5 (3·7–10)	n.s.
Surgeons' opinion				
Optimal score on HWES (%)	77	97	67	0·05‡
Cosmetic VAS*	9·3 (3·2–10)	8·0 (6·0–9·2)	6·9 (3·0–9·6)	< 0·05§
Cost per patient (€)*	34·01(15·33–61·99)	17·82 (3·32–63·46)	8·68 (2·64–43·60)	< 0·001§¶**

*Values are median (range). HWES, Holland Wound Evaluation Score; BIQ, Body Image Questionnaire; VAS, visual analogue scale; n.s., not significant. †Kruskal–Wallis test; ‡χ^2 test; §octylcyanoacrylate *versus* adhesive papertape, ¶octylcyanoacrylate *versus* poliglecaprone, **poliglecaprone *versus* adhesive papertape (Mann–Whitney U test)

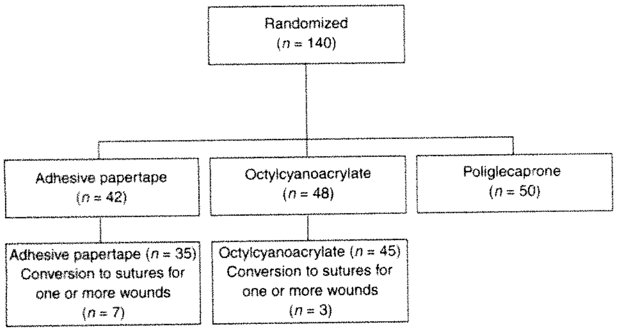
Randomized
(n = 140)
Adhesive papertape
(n = 42)
Octylcyanoacrylate
(n = 48)
Poliglecaprone
(n = 50)
Adhesive papertape (n = 35)
Conversion to sutures for one or more wounds
(n = 7)
Octylcyanoacrylate (n = 45)
Conversion to sutures for one or more wounds
(n = 3)

Fig. 1 Trial profile

The wound infection rate was highest in the octylcyanoacrylate group (10 per cent). Most wound infections occurred after laparoscopic cholecystectomy (eight of ten patients in total with a wound infection), in particular at the incision through which the gallbladder was removed. The incidence of wound infection after laparoscopic cholecystectomy (n = 70) for the whole group of patients was 11 per cent. There were no statistical differences in wound infection rate between the closure groups.

There were no differences in cosmetic result after 3 months between the three groups, as assessed by the patients, both by the cosmetic VAS score and the cosmetic scale of the BIQ (range 3–24). In the surgeons' opinion octylcyanoacrylate gave the best cosmetic result, as indicated by the highest VAS score; adhesive papertape was rated significantly lower. Wound scores, according to the HWES, were noted at 3 months. In the octylcyanoacrylate group 77 of the total of 133 wounds (n = 34) were scored; of these 77 wounds, 77 per cent (n = 59) were given an optimal score. In the poliglecaprone group 39 of the 122 wounds (n = 32) were scored; of these 39 wounds, 97 per cent (n = 38) had an optimal score. In the adhesive papertape group 43 of the 81 wounds (n = 22) were scored, of which 67 per cent (n = 29) received the optimal score (P = 0·05).

The cost of closure was €34·01, €17·82 and €8·68 per patient for octylcyanoacrylate, poliglecaprone and adhesive papertape respectively. Octylcyanoacrylate was significantly more expensive than poliglecaprone and adhesive papertape (P < 0·001), and poliglecaprone was significantly more expensive then adhesive papertape (P < 0·001).

A TMA was performed in the 106 patients treated in the Academic Medical Center. The total number of actions needed to close the wound and the number of failures were the lowest in the octylcyanoacrylate group. The greatest number of failures was noted when adhesive papertape was used (*Table 4*).

Most surgeons considered octylcyanoacrylate and adhesive papertape the fastest methods of closure (*Table 5*). Octylcyanoacrylate and adhesive papertape were also classified as very practical more often than poliglecaprone.

Discussion

This is the first prospective randomized trial to compare methods of closure in elective laparoscopic surgery. It shows that both octylcyanoacrylate and adhesive papertape are effective in closing trocar incisions. Octylcyanoacrylate, compared with poliglecaprone and adhesive papertape, requires the lowest number of actions to close a laparoscopic trocar incision. Closing with adhesive papertape was a quicker method, but it was associated with a greater

Table 4 Time–motion analysis in 106 procedures

	Octylcyanoacrylate ($n = 35$)	Poliglecaprone ($n = 39$)	Adhesive papertape ($n = 32$)
No. of actions per wound per patient	5·7 (3·7–17)*	21·0 (13–42)	8·3 (3·4–31·5)*†
No. of failures per wound per patient	0 (0–12)	0·25 (0–17)	0·23 (0–24)

Values are median (range). $^*P < 0·01$ *versus* poliglecaprone, $^\dagger P = 0·05$ *versus* octylcyanoacrylate (Mann–Whitney U test)

Table 5 Surgeons' opinion on time needed to close and practicality of material used

	Octylcyanoacrylate ($n = 48$)	Poliglecaprone ($n = 50$)	Adhesive papertape ($n = 42$)
Time needed to close (%)			
Not too long	79·2	61·2	78·6
A little too long	18·8	38·8	14·3
Far too long	2·1	0	7·1
Practicality (%)			
Very practical	41·7	26·5	50·0
Not very practical	52·1	73·5	35·7
Not practical	6·3	0	14·3

number of failures. Closing with poliglecaprone was the most ineffective and time-consuming method, according to this TMA.

The cosmetic result after 3 months, as scored by the patients, was no different between the three methods of closure. According to the surgeons, the cosmetic VAS score was significantly better for octylcyanoacrylate than adhesive papertape. However, wounds closed with poliglecaprone were scored 'optimal' on the HWES, an objective wound score, more often than those closed with octylcyanoacrylate or adhesive papertape. The cosmetic results of adhesive papertape scored lowest on both the VAS score and the HWES. Examining the results in *Table 3*, it might be concluded that there is a difference in opinion between the surgeon and the patient with respect to the cosmetic result. The surgeon sees hundreds of wounds and has a different frame of reference from that of the patient, who is only able to judge his or her own wounds. However, the patient's opinion should be considered more important than that of the surgeon because the patient has to live with the scars. Quinn *et al.*[10] showed in a randomized trial that cosmetic outcome 1 year after wound closure was no different for octylcyanoacrylates and for sutures in closure of traumatic lacerations.

Octylcyanoacrylate and adhesive papertape were scored as more practical and less time consuming than poliglecaprone; there was no difference between octylcyanoacrylate and adhesive papertape.

Wound infection was seen more often after laparoscopic cholecystectomy and in all these patients the infection occurred in the wound through which the gallbladder was removed. The incidence of wound infection was 11 per cent; published rates vary from 0·5 to 10 per cent, the higher rates being reported in randomized trials[11–14]. These wound infections may have resulted from sealing a contaminated wound, especially after the use of octylcyanoacrylates. However, Quinn *et al.*[15] showed that octylcyanoacrylate is associated with fewer wound infections than sutures in a contaminated wound model. Several other studies have showed the antimicrobial effect of tissue adhesives[16–19].

In a prospective study Chen *et al.*[1] showed that papertape closure in colorectal surgery was faster and more cost-effective then suturing, and was associated with greater patient satisfaction with the cosmetic result. In contrast, Rosen and Carlton[20] stated that adhesive papertape is unsuitable for skin closure of laparoscopic incisions because patients had more postoperative pain and were less satisfied with the cosmetic result, and there was a slightly higher infection rate. The use of a tissue adhesive is recommended by Rosin *et al.*[6] mainly because the risk of needle-stick injuries is eliminated. They also showed low infection rates and good cosmetic results in their study population.

The use of octylcyanoacrylate for closing trocar incisions was significantly more expensive than the use of poliglecaprone or adhesive papertape. The use of adhesive papertape was by far the cheapest closing method. In this study a median of two ampoules of octylcyanoacrylate were used to close trocar wounds. One can assume that closing trocar incisions can be done with one ampoule of octylcyanoacrylate, so reducing costs.

In an emergency department setting and in children[2,4,10] octylcyanoacrylate has been demonstrated to be an effective method of closure for low-tension wounds or surgical incisions. In these cases octylcyanoacrylate might be cost-effective because there are no costs for anaesthetics and sterilizing surgical instruments.

In conclusion, closure of laparoscopic trocar wounds with octylcyanoacrylate required fewer actions, but was the most expensive of the three methods tested. Adhesive papertape was the most cost-effective, because it is was the fastest and cheapest method.

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Randomized clinical trial of stapled haemorrhoidopexy *versus* conventional diathermy haemorrhoidectomy

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Background: The aim of this study was to compare the results of stapled haemorrhoidopexy (commonly called stapled haemorrhoidectomy) with those of conventional diathermy haemorrhoidectomy.
Methods: Fifty-five patients with symptomatic third- and fourth-degree haemorrhoids were randomized to either stapled haemorrhoidopexy ($n = 27$) or conventional diathermy haemorrhoidectomy ($n = 28$). Operating time, postoperative pain, time to return to work, postoperative complications and effectiveness of haemorrhoidal symptom control were recorded. The mean follow-up was 15·9 months in the stapled haemorrhoidopexy group and 15·2 months in the conventional haemorrhoidectomy group.
Results: Mean pain intensity was significantly less in the stapled group ($P = 0{\cdot}001$). There were no significant differences in the total number of complications, the length of absence from work or control of symptoms. Seven patients in the stapled group re-presented with prolapse compared with none in the conventional haemorrhoidectomy group ($P = 0{\cdot}004$). This difference was also observed in the subset of patients with fourth-degree haemorrhoids ($P = 0{\cdot}003$).
Conclusion: The stapled operation was significantly less painful than conventional haemorrhoidectomy. However, the rate of recurrent prolapse was higher after stapled haemorrhoidopexy than after conventional diathermy haemorrhoidectomy.

Paper accepted 28 June 2002

British Journal of Surgery 2002, **89**, 1376–1381

Introduction

Haemorrhoidectomy almost always cures haemorrhoids[1], but conventional excision of symptomatic prolapsed haemorrhoids is a notoriously painful operation. Most patients have pain on defaecation and discomfort at rest in the second and third weeks after operation from wound infection and anal sphincter spasm. Technical modification to decrease postoperative pain has included the addition of lateral internal sphincterotomy[2], closed haemorrhoidectomy[3], diathermy haemorrhoidectomy[4], and use of anal sphincter relaxants[5] or metronidazole[6]. Although all of these techniques have had their advocates, none has resulted in a sufficient decrease in postoperative pain to gain universal acceptance.

A new approach to the treatment of haemorrhoids, proposed by Longo[7], is a transverse mucosal prolapsectomy using a circular stapling device at the anorectal angle at a distance between 3 and 4 cm above the dentate line. This technique involves interruption of the terminal branches of the superior haemorrhoidal arteries and resection of part of the prolapsed mucosa. This lifts the mucosa up in the anal canal, thus correcting the prolapse and reducing the arterial inflow. Stapled haemorrhoidopexy (commonly called stapled haemorrhoidectomy), as advocated initially, has been associated with a significant change in the treatment approach of haemorrhoids. The value of stapled haemorrhoidopexy as an alternative to conventional haemorrhoidectomy has been assessed in a number of randomized controlled trials[8–15]. These studies have consistently shown that the Longo procedure is a simple, safe and effective method that results in a shorter recovery time and earlier return to work. The postoperative recurrence rate is reported to be similar to that after the excisional technique. Although more expensive[10], the results are promising[16–19] and, provided that further clinical trials confirm these findings, stapled haemorrhoidopexy may become the standard of care[17]. The present randomized clinical trial was designed to compare stapled haemorrhoidopexy with conventional diathermy haemorrhoidectomy with regard to operating time, postoperative pain, time to return to work, postoperative complications, functional outcome and effectiveness in symptom control in patients with prolapsing haemorrhoids.

Patients and methods

Between November 1999 and December 2000, 55 consecutive patients with symptomatic third-degree ($n = 29$) and fourth-degree ($n = 26$) haemorrhoids[20] were enrolled in the study. The protocol was approved by the institutional review board and patients gave written informed consent to participate in the study. Exclusion criteria included concomitant anal disease (fissure, abscess, fistula, incontinence, inflammatory bowel disease and dermatitis), previous anal surgery, patients receiving treatment with oral anticoagulants and American Society of Anesthesiologists grade III or IV. Patients over the age of 50 years underwent a colonoscopy before haemorrhoidectomy.

Patients were assigned randomly to the circular stapled procedure ($n = 27$) or to conventional diathermy haemorrhoidectomy ($n = 28$) by a computer-generated table of random numbers. All operations were performed without bowel preparation, under spinal anaesthesia and with the patient in the lithotomy position, by a specialist colorectal surgeon (H.O.). The intraoperative time was measured with a chronometer. To avoid a 'learning curve' effect, the principal surgeon had performed 25 stapled operations before commencing the trial[21].

The stapled procedure was performed according to the technique described by Longo[7]. A purse-string suture of 2/0 polypropylene was inserted between 3 and 4 cm above the dentate line, catching only the mucosa and submucosa (at 3 cm to get adequate lifting of large haemorrhoids but closer to 4 cm to remove redundant and prolapsing rectal mucosa in the relative absence of haemorrhoids). The PPH01™ stapling gun (a 33-mm haemorrhoidal circular stapling device) (Ethicon Endosurgery, Madrid, Spain) was used throughout. The PPH01™ stapling gun was opened to its maximum position and introduced through the anus. The purse-string suture was tied on the stapler shaft, and the head of the instrument was closed on the anvil, incorporating the mucosal tissue in the purse-string within the head of the gun. The stapler was then fired and gently withdrawn. To get optimal fixation of prolapsing haemorrhoids the staple line must be directly above the haemorrhoid pedicle. The staple line was inspected for bleeding. Actively spurting vessels were suture ligated (4/0 polyglactin). No haemostatic dressings were left in the anal canal at the end of the procedure.

Conventional diathermy haemorrhoidectomy was performed using a Ferguson retractor. It was used to open up the anus gently and to display the full extent of the haemorrhoid. The external and internal components were excised entirely up to the anorectal ring with high-current electrocautery. The pedicle was excised without suture ligation and haemostasis achieved with diathermy. No packs were left in the anal canal at the end of the procedure. The excised tissue was sent for histopathological analysis.

Postoperative scheduled analgesia consisted of dipyrone (575 mg four times daily by mouth) and diclofenac (100 mg twice daily by mouth). Intravenous tramadol (100 mg three times daily) was administered as rescue analgesia. A 100-mm visual analogue scale, from 0 (no pain) to 10 (the worst pain imaginable), was used to evaluate the intensity of pain. The pain score was recorded every 12 h during the first 3 days, then daily until 10 days after operation. Peak pain (defaecation pain) was not measured.

Patients were discharged from hospital 3 days after the operation in accordance with the unit policy at the time of the study, once they required no further intravenous analgesia. Before hospital discharge, an independent blinded observer assessed analogue pain score and analgesic requirements. Patients were discharged with a package of postoperative care that included oral metronidazole, diclofenac and dipyrone. Patients were given an advice sheet and telephone number in case of emergency.

Clinical evaluation was repeated at 14 days, 6 weeks, 4 months, 1 year and once more when the last patient included had been followed up for 1 year after surgery. The outcome measures were operative time, postoperative pain, frequency of rescue analgesia, time to return to normal activity, complications, control of haemorrhoidal symptoms and patient's degree of satisfaction. Continence was scored on a scale of 1–20, according to the incontinence score system of Jorge and Wexner[22], before operation and 1 year after surgery. A 100-mm visual analogue scale was used to evaluate patient's degree of satisfaction, where 0 corresponded to a unsatisfactory result and 10 to an excellent result. All data were recorded by an independent observer who was unaware of the operation performed.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (version 10) statistical package (SPSS, Chicago, Illinois, USA). The Mann–Whitney U test was used for the comparison of postoperative pain intensity and age of patients, and χ^2 test and two-tailed Fisher's exact test for comparison of categorical data. The sample size was established before the study. In a pilot study of patients undergoing conventional haemorrhoidectomy at this hospital, the mean(s.d.) postoperative pain on the visual analogue scale was 25(16) mm. According to these findings, approximately 27 patients in each arm were calculated to be

Table 1 Baseline characteristics of patients

	Stapled (*n* = 27)	Conventional (*n* = 28)
Mean(s.d.) age (years)	48·6(11·5)	46·6(11·2)
Sex ratio (M : F)	15 : 12	17 : 11
Degree of haemorrhoids		
Third	17	12
Fourth	10	16
Symptom of haemorrhoids		
Prolapse	27	28
Bleeding	24	25
Itching	17	19
Pain	14	14
Incontinence	0	0

There were no significant differences between the groups

Table 2 Operating time and postoperative complications

	Stapled (*n* = 27)	Conventional (*n* = 28)
Operating time (min)*	19·0 (14–35)	33·5 (15–90)‡
Time to first motion (days)*	2·9 (0–5)	3·2 (1–6)
Postoperative pain (mm)*†	11·9 (0–22·9)	34·6 (10·9–62·2)§
Postoperative complications	10	12
Retention of urine	6	10
Secondary haemorrhage		1
Difficult evacuation	1	
Septic complications	1	1
Thrombosed residual haemorrhoid	1	
Persistent pain	1	
Return to work activities (weeks)*	3·3 (0–14)	3·8 (0–16)

*Values are mean (range). †Visual analogue scale. ‡*P* = 0·001, §*P* = 0·007 *versus* stapled (Mann–Whitney *U* test)

necessary to detect an expected 50 per cent reduction in postoperative pain. An alpha error of 5 per cent and a beta error of 20 per cent were accepted.

Results

The patients' baseline demographic and clinical data are shown in *Table 1*. The two groups were well matched for age, sex and symptoms of haemorrhoids. There was an imbalance in the severity of haemorrhoids between groups, with less severity in the stapled group, although this was not statistically significant (*P* = 0·1)

Operative time and intraoperative complications

The time taken to perform stapled haemorrhoidopexy was significantly less than that for conventional diathermy haemorrhoidectomy (mean (range) 19·0 (14–35) *versus* 33·5 (15–90) min; *P* = 0·001). Haemostatic sutures were required in 19 patients to control minor staple-line bleeding points. Eleven patients required one stitch, seven patients two stitches and one patient three stitches.

Histopathology

Examination of the excised tissue showed some rectal smooth muscle fibres in seven cases in the stapled haemorrhoidopexy group. In the conventional diathermy haemorrhoidectomy procedure, no internal anal sphincter muscle was found.

Postoperative outcome

There were no differences between the two groups in time to the first bowel movement (*Table 2*). All patients received analgesia in the postoperative period. The mean pain scores were significantly lower in the stapled haemorrhoidopexy group during the first 14 days. Mean pain intensity was 11·9 (range 0–22·9) mm in the stapled group and 34·6 (range 10·9–62·2) mm in the conventional diathermy haemorrhoidectomy group (*P* = 0·007). Eight patients, five in the conventional group and three in the stapled group, required intramuscular analgesics on the first postoperative day (*P* not significant).

Complications

No patient presented with residual mucosal or haemorrhoidal prolapse immediately after operation. Early postoperative complications in the stapled group included acute urine retention (six patients), external haemorrhoidal thrombosis 2 days after operation (one) and faecal impaction 4 days after haemorrhoidopexy (one). One patient complained of the passage of pus from the rectum on the sixth postoperative day; digital examination revealed partial dehiscence of the suture and antibiotic therapy was instituted. Persistent pain over 14 weeks was reported by one patient. In the conventional diathermy haemorrhoidectomy group, postoperative complications included postoperative urinary retention, bleeding 7 days after the operation that requiring suture ligation under general anaesthesia (one), and development of a subcutaneous fistula in a wound 6 weeks after operation (one). There were no significant differences between groups in the total number of complications noted (*Table 2*).

Return to working activities

All patients were of working age. The length of absence from work was 3·8 (range 0–16) weeks in the conventional

Table 3 Clinical results

	Stapled (n = 27)	Conventional (n = 28)
Prolapse	7	0†
Haemorrhage	2	1
Itching	3	2
Pain	1	0
Urgency	2	4
Skin tags	7	7
Incontinence	0	0
Patient's satisfaction*	7·6 (0–10)	9·3 (6–10)

*Mean (range) score on visual analogue scale. †P = 0·004 *versus* stapled (Fisher's exact test)

diathermy haemorrhoidectomy group and 3·3 (range 0–14) weeks in the stapled haemorrhoidopexy group (P not significant).

Long-term evaluation

All patients were available at the end of follow-up (*Table 3*). The mean follow-up period was 15·9 (range 12·2–24·6) months in the stapled haemorrhoidopexy group and 15·2 (12·4–23·2) months in the conventional diathermy haemorrhoidectomy group (P not significant). Clinically, there were no significant differences with respect to the persistence of bleeding, itching, pain, urgency and skin tags between the two groups. No faecal incontinence or stenosis was reported in either group. However, recurrent prolapse starting from the fourth month after operation (true recurrence) was reported and confirmed by clinical examination in seven patients in the stapled group, whereas none in the conventional diathermy haemorrhoidectomy group experienced this symptom (P = 0·004). Prolapse was assessed according to the degree of haemorrhoids. Among patients with third-degree haemorrhoids, two of 17 patients in the stapled group had recurrent prolapse compared with none in the conventional diathermy group (P = 0·49; relative risk 0·08 (95 per cent confidence interval (c.i.) 0·74 to 1·05)). Among patients with fourth-degree haemorrhoids, five of ten patients in the stapled group and none in the conventional diathermy group had this symptom (P = 0·003; relative risk 0·50 (95 per cent c.i. 0·27 to 0·93)).

There were no significant differences in the degree of patient satisfaction. However, after 1-year follow-up, three patients in the stapled group rated their symptom control as unsatisfactory owing to persistence of prolapse. These patients, however, responded well to a later conventional diathermy haemorrhoidectomy.

Discussion

Stapled haemorrhoidopexy (haemorrhoidectomy), first described by Longo[7], is a novel approach to the surgical management of haemorrhoids. Several studies that have compared the stapled technique with conventional haemorrhoidectomy have highlighted the promising results of the stapled technique[8–19]. In only two of these reports[11, 12] have patients been followed up for 1 year or more.

The stapling procedure itself took a mean of 19 min, which is similar to that reported by others[8–12]. The percentage of cases in which supplementary haemostatic sutures were necessary is surprisingly high, particularly as bleeding from the anastomosis occurs infrequently following low anterior resection with stapled anastomoses[23]. A possible explanation is the design or staple height of the PPH01™ device.

The current study has shown that pain was significantly less after stapled compared with conventional haemorrhoidectomy. This is in agreement with previous randomized controlled trials[8–19]. In contrast, there were no significant differences in the mean time to return to work, a less favourable outcome than that reported previously[8–12]. None the less, social and cultural factors need to be taken into account in the assessment of return to work as well as hospital discharge.

The results of the present series indicate that the frequency, type and severity of postoperative complications were similar with both techniques. Moreover, only one patient in the conventional diathermy group required emergency examination under anaesthesia. This is consistent with the findings of previous randomized trials[8–12]. Other complications associated with stapling reported anecdotally are severe retroperitoneal sepsis[24] and rectovaginal fistula[25].

A patient in the current series presented with pain that persisted for up to 3 months after stapled haemorrhoidopexy. Cheetam *et al.*[15] reported that five of 16 patients developed persistent pain and faecal urgency, which persisted for up to 15 months after stapled haemorrhoidopexy. This is difficult to understand as other authors have found no persistent pain after the stapled procedure. In the present study, the cause of this phenomenon is unclear; muscular fibres were not found in the excised tissue and the stapled suture was at least 2 cm above the dentate line.

The aim of this study was not only to compare postoperative pain but also to assess the effectiveness of each technique as a definitive cure for haemorrhoids. Resolution of haemorrhoidal symptoms, including bleeding, itching, pain and residual components of external haemorrhoids, was equivalent in the two groups. However, recurrent prolapse was significantly more common after stapled haemorrhoidopexy than after conventional haemorrhoidectomy. The recurrence cannot immediately be ascribed to technical inexperience. Moreover, in this study recurrent prolapse was significantly more frequent in patients with fourth-degree haemorrhoids than in patients with third-degree haemorrhoids. It may be argued that fourth-degree haemorrhoids may not represent an appropriate indication for the stapled procedure, as the success of the operation depends entirely on the reduction of the prolapse by the stapler. On the other hand, it should be noted that in the current study the severity of haemorrhoids was slightly less in the stapled group, although differences were not statistically significant. However, this imbalance only acts to diminish the failure of the stapled group.

Two studies that compared the long-term outcome of both procedures have been published. Shalaby and Desoky[12] reported recurrent prolapse in only one of 95 patients whereas Ganio *et al.*[11] reported recurrent prolapse in ten of 50 patients after the stapled procedure. However, a comparative evaluation of the results of the three studies is difficult. Shalaby and Desoky[12] included patients with second-degree haemorrhoids and with mucosal prolapse, while Ganio *et al.*[11] performed telephone follow-up. However, in the current study the patients' final perceived level of satisfaction was no different between the two procedures. This is consistent with data from previous randomized trials[11,12].

In conclusion, the circular stapled procedure for haemorrhoids is superior to conventional diathermy haemorrhoidectomy in terms of duration of operation and postoperative pain. It is a safe procedure. Early functional and symptomatic outcomes have been satisfactory and seem to be similar to those achieved using conventional techniques. However, the rate of recurrent prolapse, especially in patients with fourth-degree haemorrhoids, was higher after stapled haemorrhoidopexy than after conventional diathermy haemorrhoidectomy.

Acknowledgements

The authors thank Dr Marta Pulido for editing the manuscript and editorial assistance.

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Association of Surgeons of Great Britain and Ireland

The annual meeting of the Association of Surgeons of Great Britain and Ireland was held in Dublin, Ireland on 22–24 May 2001 under the Presidency of Mr R. W. G. Johnson. The abstracts of the presentations of the original work presented at the meeting have been published in a *BJS* supplement that accompanied the June 2002 issue of the Journal. The following articles are based on presentations from the Dublin meeting and have been accepted for publication after peer review by the Journal's referees.

Association of Surgeons

Management of popliteal aneurysm

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Background: The best management of patients with a popliteal aneurysm has yet to be established. This paper describes an experience of managing both patent and acutely thrombosed popliteal aneurysms.

Methods: A prospective study was carried out of all patients who presented with a popliteal aneurysm from January 1988 to December 2001. Since 1993 asymptomatic popliteal aneurysms less than 3 cm in diameter without distortion have been managed conservatively. Ultrasonography was repeated at 6-month intervals. These results were compared with conservative management of popliteal aneurysms greater than 3 cm in diameter in patients who declined or were unfit for operation, and with the outcome of patients who underwent elective bypass of a popliteal aneurysm.

Results: Fifty-eight patients (two women) presented with 92 popliteal aneurysms. Some 39 had a thrombosed aneurysm and these patients were significantly more likely to have bilateral aneurysms ($P < 0.001$). Of patent popliteal aneurysms managed conservatively, none below 3 cm in diameter thrombosed. The risk of postoperative complications was greater after repair of a thrombosed than a patent aneurysm ($P < 0.005$). Preoperative lysis for a thrombosed popliteal aneurysm was associated with more complications than operation and on-table lysis ($P < 0.05$).

Conclusion: Careful monitoring of asymptomatic popliteal aneurysms less than 3 cm in diameter is safe. Preoperative lysis is associated with increased risks compared with operation alone in patients with a thrombosed popliteal aneurysm.

Paper accepted 8 June 2002

British Journal of Surgery 2002, **89**, 1382–1385

Introduction

The likelihood of an asymptomatic popliteal aneurysm becoming symptomatic is approximately 14 per cent per year[1]. However, not all of these symptoms will be due to thrombosis. Thrombosis of a popliteal aneurysm is associated with leg loss in up to 30 per cent of patients[1]. Patients whose legs are saved often have residual symptoms. Elective bypass of a popliteal aneurysm is often advised to avoid these complications. However, popliteal aneurysms occur mainly in older men who have significant cardiovascular disease and a limited life expectancy[2]. These facts need to be considered when discussing elective operation.

It is not clear which popliteal aneurysms are at risk of thrombosis. Operation is often advised for aneurysms greater than 2 cm in diameter or those containing thrombus[3], but there is little hard evidence to support this treatment protocol. Amputation has occasionally been necessary after failed elective bypass[1]. There is an average graft patency of approximately 80 per cent 5 years after elective repair.

The authors previously found that size greater than 3 cm and distortion within or outside the aneurysm were significant risk factors for thrombosis[4]. Since that time all patients with an asymptomatic popliteal aneurysm have been managed conservatively until the diameter reached 3 cm, unless distortion was noted on angiography.

The aims of this paper were first to define the outcome of conservative management of asymptomatic popliteal aneurysms less than 3 cm in diameter and, second, to compare these results with elective bypass of the aneurysm. Finally, the management and outcome following popliteal aneurysm thrombosis is described.

Patients and methods

Popliteal aneurysm was defined as a localized dilatation of the popliteal artery greater than 2 cm in diameter or greater than 150 per cent of the normal proximal arterial calibre[5,6]. All patients with a popliteal aneurysm who presented between January 1988 and December 2001 were included. Data were collected prospectively and missing information was obtained by referral to case notes.

Clinical management changed during the study. All patients had ultrasonography of the popliteal fossa and intravenous or intra-arterial digital subtraction angiography to define the anatomy and run-off. Patients who presented electively and were not offered immediate repair had ultrasonography every 6 months. Elective repair was offered if the aneurysm became symptomatic. For aneurysms that remained asymptomatic elective repair was advised if the aneurysm reached more than 2 cm in diameter until January 1993. From then, in the absence of distortion, the size threshold for advising repair was increased to 3 cm. For patients who presented with a thrombosed popliteal aneurysm, operation was carried out as an emergency or urgent procedure until November 1988. Following introduction of intra-arterial thrombolysis, these patients were managed by lysis followed by operation[7,8]. From September 1992, patients with a thrombosed aneurysm were offered urgent or emergency operation combined with on-table thrombolysis.

Statistical analysis was carried out using the χ^2 test. Patency following operation and the likelihood of symptoms developing with conservative treatment were analysed using the Kaplan–Meier and log rank tests.

Results

In the 14 years, 58 patients presented with 92 atherosclerotic popliteal aneurysms. Median follow-up was 50 months (range 3 months to 11 years). There were two women. The median age of the patients was 68 (range 46–86) years. Some 39 patients presented with a thrombosed aneurysm. Demographic details are shown in *Table 1*. Patients with a thrombosed popliteal aneurysm were significantly more likely to have bilateral aneurysms (28 of 39 *versus* 4 of 19; $\chi^2 = 13{\cdot}3$, 1 d.f., $P < 0{\cdot}001$). Overall 25 patients (43 per cent) had an associated abdominal aortic aneurysm. There was no difference in the prevalence of aortic aneurysm in patients with thrombosed or patent popliteal aneurysms. Significant cardiovascular disease was noted in 40 (69 per cent) of the 58 patients.

Table 1 Comparison of demographic data in patients with popliteal aneurysms that presented either thrombosed or patent

	Thrombosed	Patent
No. of patients	39	19
Sex ratio (M : F)	38 : 1	18 : 1
Median (range) age (years)	69 (47–86)	66 (46–86)
Other aneurysm present		
Aortic	19	6
Contralateral popliteal	28	4*
Femoral	1	1

*$P < 0{\cdot}001$ *versus* thrombosed (χ^2 test)

Of 39 aneurysms that had thrombosed, 30 presented acutely (acute ischaemia in 28 and sudden claudication in two). Five patients presented with rest pain or gangrene, two with chronic claudication and two had an asymptomatic occlusion. The latter two patients were being investigated for symptoms in the other leg when the thrombosed aneurysm was discovered. In two patients the popliteal aneurysm had been misdiagnosed. One presented with leg ulceration that had been diagnosed and treated as due to a deep venous thrombosis. The other had been thought to have a Baker's cyst some months before thrombosis.

Asymptomatic popliteal aneurysm

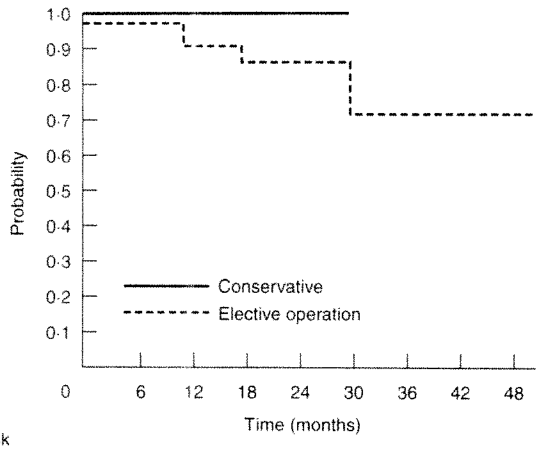
None of the patients with a popliteal aneurysm less than 2 cm in diameter developed thrombosis or any other symptoms. Seven patients who had a an aneurysm greater than 3 cm in diameter either declined operation or were unfit for the procedure. One of these patients subsequently died, in three the aneuyrsm thrombosed, and three others developed discomfort behind the knee. None of seven popliteal aneurysms in the 2–3-cm group thrombosed and only one developed symptoms (discomfort and swelling of the calf). No statistically significant difference was seen with respect to either thrombosis or symptom development in this small group of patients ($P = 0{\cdot}37$ and $P = 0{\cdot}32$, respectively).

Surgical repair

Operation was carried out for 55 of the 92 popliteal aneurysms. There were 30 vein grafts (23 popliteal–

Table 2 Thirty-day results after bypass for popliteal aneurysm (55 procedures)

	Total	Amputation	Died	Other complication
Thrombosed popliteal aneurysm	36	4	1	13
Operation alone or on-table lysis	22	4	0	5
Preoperative lysis	14	0	1	8
Elective repair of patent popliteal aneurysm	19	0	0	0



No. at risk								
Conservative	7	6	5	3	3			
Elective operation	18	18	14	13	13	11	8	8

Fig. 1 Comparison of likelihood of thrombosis of popliteal aneurysms 2–3 cm in diameter treated conservatively with those having elective bypass

popliteal, five femoropopliteal and two femorotibial). Synthetic material was used in 25 procedures (15 popliteal–popliteal, ten femoropopliteal). *Table 2* shows 30-day results. Four patients with a thrombosed aneurysm underwent major amputation after failed bypass. No patient who had elective repair required amputation. Some 17 major complications were seen. These included four episodes of haemorrhage, acute leg deterioration during lysis in three patients and two myocardial infarctions, one of which was fatal. Two patients developed foot drop despite fasciotomy, one patient had a deep venous thrombosis and five had wound infections. No significant complications were seen in the 19 patients who had elective operation. This compared with complications in 13 of 36 thrombosed popliteal aneurysms ($\chi^2 = 8{\cdot}9$, 1 d.f., $P < 0{\cdot}005$). Complications were more common in those with a thrombosed aneurysm who had preoperative lysis than in patients who underwent operation alone ($\chi^2 = 4{\cdot}4$, 1 d.f., $P < 0{\cdot}05$).

The type of operation had no influence on graft patency. There was no difference in patency rates in patients who had elective repair of symptomatic (patent) compared with asymptomatic aneurysms (3-year graft patency 70 and 80 per cent respectively; $P = 0{\cdot}63$). For patients whose aneurysm had thrombosed, preoperative lysis had no overall benefit compared with operation alone; 3-year graft patency rate was 76 and 67 per cent respectively ($P = 0{\cdot}29$). Following elective repair, graft patency at 3 years was 73 per cent compared with 71 per cent following repair of a thrombosed aneurysm ($P = 0{\cdot}42$). When the likelihood of thrombosis of a popliteal aneurysm 2–3 cm in diameter treated conservatively was compared with graft patency following elective repair, there was no significant difference ($P = 0{\cdot}59$) (*Fig. 1*). Patients treated conservatively fared no worse than those who had elective operation.

A total of six patients died during follow-up, including five who had bypass of a thrombosed popliteal aneurysm and one who was deemed unfit for repair of an aneurysm greater than 3 cm in diameter.

Discussion

Rupture of a popliteal aneurysm, although potentially life threatening, is rare; it is thrombosis, resulting in an acutely ischaemic leg, that most concerns vascular surgeons. Once thrombosis occurs there is a significant risk of death and amputation of approximately 5 per cent and up to 30 per cent respectively[1].

Although lysis of a thrombosed popliteal aneurysm has been recommended, it is not without risks. Stroke and major bleeding occur in 1 and 5 per cent of patients respectively[9]. Furthermore, acute deterioration of the leg during lysis due to destabilization of a large volume of thrombus seems to be a particular risk in popliteal aneurysms[10]. Complications were significantly more likely with preoperative lysis in this series compared with operation alone. There was no significant increase in long-term patency, although others have suggested that the patency rate following successful thrombolysis of a thrombosed popliteal aneurysm is greater than that after early operation alone (W. Dorigo, R. Pulli, F. Turini, G. Pratesi, G. Credi, A. A. Innocentia, C. Pratesi, unpublished observation). However, lysis can clear run-off effectively and it has been suggested that lysis followed by anticoagulation may be all that is required to preserve the leg[11]. Early exploration and lysis of run-off during operation, if necessary, seems a more attractive alternative[12].

The average 5-year patency following elective popliteal aneurysm bypass is approximately 80 per cent[1]. This compares with 65 per cent for bypass after operation for symptomatic popliteal aneurysm. However, respective reported ranges for patency rate are 70–94 and 50–80 per cent. The evidence suggests that patency is greater after elective bypass. Limb salvage is certainly better than that after bypass for thrombosed popliteal aneurysm[13].

The 5-year survival rate of patients with popliteal aneurysm is approximately 60 per cent[1]. Only six (10 per cent) of 58 patients died in the present series at a median follow-up of 50 months. Nevertheless significant cardiovascular disease was identified in over two-thirds. In addition nearly half of the patients had an aortic aneurysm. Clearly patients with a popliteal aneurysm represent a high-risk group. Operation should be avoided unless the risk of popliteal aneurysm thrombosis is high.

Varga *et al.*[14] showed that the average diameter of an asymptomatic popliteal aneurysm was 2 cm, while that of a popliteal aneurysm producing ischaemic symptoms was 3 cm. In a previous study thrombosed aneurysms were found to be larger and were more likely to have distortion either within, or outside, the aneurysm compared with those that were asymptomatic[2]. The combination of distortion and size greater than 3 cm was present in 13 of 15 thrombosed aneurysms. Construction of a Markov decision tree showed that, at an average rate of any symptom development (not only thrombosis) of 14 per cent per year, it was 16 months following elective operation that the operation became beneficial[1].

As the aneurysm enlarges, mural thrombus develops[14]. Cited indications for elective repair include popliteal aneurysm greater than 2 cm in diameter, those containing thrombus, or where run-off is poor[3,15]. There is little evidence to support this. Popliteal aneurysms less than 2 cm seem to be at low risk of thrombosis[16]. Similarly, there seems little to be gained by delaying elective repair in an otherwise fit patient with an aneurysm greater than 3 cm in diameter. All popliteal aneurysms greater than 3 cm in diameter became symptomatic in the present series. This compares with seven of ten large aneurysms causing symptoms after 3-year follow-up described by Dawson *et al.*[17]. The present data suggest that popliteal aneurysms under 3 cm in diameter can safely be observed, with little chance of thrombosis. No aneurysm of this size thrombosed and only one became symptomatic during follow-up. The likelihood of thrombosis was less (but not significantly so) than that following elective bypass.

Providing that a popliteal aneurysm less than 3 cm in diameter is asymptomatic and shows no sign of distortion, prophylactic reconstruction may not be necessary. Careful follow-up is mandatory and development of symptoms or enlargement to more than 3 cm diameter warrants early reconstruction.

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Evaluation of axillary lymph nodes using touch imprint cytology and immunohistochemistry

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Background: The success of sentinel node biopsy in determining axillary lymph node status necessitates an accurate and rapid method for intraoperative examination of the nodes. The aim was to determine the feasibility and accuracy of immunohistochemistry (IHC) of touch imprints in detecting axillary nodal metastases intraoperatively.
Methods: Some 344 axillary nodes from 30 patients with early breast cancer were bisected, imprinted and subjected to IHC. Results were compared with those of routine haematoxylin and eosin examination of the same nodes.
Results: Using IHC, 29 nodes from nine patients were positive for metastases. Using haematoxylin and eosin, 28 nodes from eight patients were positive. On a patient basis, the sensitivities of IHC and haematoxylin and eosin were 100 and 88·9 per cent, and negative predictive values (NPVs) were 100 and 95·5 per cent, respectively. On a node basis, the sensitivities were 96·7 and 93·3 per cent, and NPVs were 99·7 and 99·3 per cent, respectively. There were no false positives. The results were obtained within 30–45 min, depending on the number of nodes examined.
Conclusion: IHC of touch imprints can provide a fast and sensitive method for detecting metastases in axillary nodes during breast cancer surgery.

Paper accepted 18 June 2002

British Journal of Surgery 2002, **89**, 1386–1389

Introduction

Sentinel node biopsy is an accurate predictor of axillary node status[1–5]. Intraoperative evaluation of the sentinel lymph nodes (SLNs) enables a surgeon to decide whether to proceed to an axillary node clearance at the same operation. This spares the patient a further admission to hospital and another anaesthetic, and reduces costs. Intraoperative evaluation of the SLN may be achieved by histological examination of frozen-section biopsies or by imprint cytology. Many investigators have studied frozen sections in the intraoperative evaluation of SLNs[1,3,6–8]. Conventional frozen section was reported initially to be inadequate, because of high false-negative rates[3,6,7]. The use of serial sectioning and/or immunohistochemistry (IHC) has improved the accuracy of frozen-section analysis[1,8]. The disadvantage of serial sampling of frozen sections is the loss of tissue for definitive histology[9,10]. The accuracy rate of imprint cytology in detecting axillary metastases intraoperatively is high[7,11–13], but the need for an experienced cytologist might preclude its widespread use[14].

Staining touch imprints with anticytokeratin IHC might improve the accuracy of imprint cytology in the intraoperative evaluation of SLNs. The aim of this study was to determine the feasibility of rapid immunostaining of touch imprints with anticytokeratin 19 and to establish a working staining protocol to provide consistent and reproducible results.

Materials and methods

Patients

Thirty women with early breast cancer (stage I or II) took part in this study. Node tissue was retrieved as part of standard breast cancer surgery including axillary node clearance, sampling or sentinel node biopsy.

Approval was obtained from the local research ethics committee before the start of the study, and all patients were

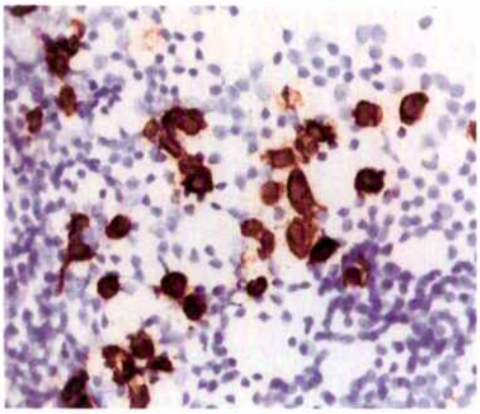

Fig. 1 Immunohistochemically stained cancer cells in an imprint (original magnification × 400)

given an information sheet and gave written informed consent.

Pathological procedures

The lymph nodes were dissected clear of fat and washed in distilled water to remove red blood cells, then dried by wrapping in dry gauze. Each node was cut using a fresh knife blade along the longest plane to expose the maximum surface area. The fresh cut surface was imprinted on a series of five positively charged slides (SuperFrost® Plus; Menzel-Glaser, Germany) and air-dried for 2 min, then fixed and stained according to the protocol below. The nodes were sent to the laboratory for routine processing.

Immunostaining

Staining of the imprints was performed according to a protocol of rapid immunostaining developed in this department[15]. In brief, the slides were fixed in fresh acetone for 2 min, then washed in buffer solution for 30 s three times. The slides were incubated with Enhanced Polymer One-step Staining reagent (anticytokeratin 19, clone RCK108; DAKO, Glostrup, Denmark) at 37°C for 5 min, then washed again in buffer solution for 30 s three times and incubated with diaminobenzidine chromogen (kit from BioGenex, San Ramon, California, USA) at 37°C for 5 min. Next the slides were washed in running water for 30 s. The nuclei were stained with haematoxylin for 30 s and washed in running water for 30 s then dehydrated in alcohol three times and xylene twice for 30 s. Finally, the slides were mounted and read by an experienced cytopathologist. At least two imprints were stained for initial reading from each node, together with positive and negative controls.

Cytopathology

An immunostained imprint was considered positive if at least one group of no fewer than six coherent cancer cells was seen within the node tissue (*Fig. 1*). If immunostained touch imprints were positive while the permanent haematoxylin and eosin-stained paraffin sections were negative, immunostained paraffin sections were prepared to confirm the results.

Statistical analysis

Results of immunohistochemically stained touch imprints were compared with those of standard haematoxylin and eosin-stained paraffin sections. Statistical calculations were done using sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), for both staining methods. Confidence intervals for proportions and paired differences of proportions were calculated using methods described by Wilson[16] and Newcombe[17].

Results

The 30 women included in the study had a mean age of 58 (range 32–88) years. Node tissue was retrieved from axillary node clearance in 23, axillary node sampling in two and sentinel node biopsy in five women. Twenty-five women had invasive ductal carcinoma and five had invasive lobular carcinoma. Tumour size ranged from 3 to 80 (mean 23) mm.

A total of 344 axillary nodes were examined using both immunohistochemically stained touch imprints and haematoxylin and eosin-stained paraffin sections: 29 nodes from nine patients contained metastases on immunostained imprints and 28 nodes from eight patients were positive on haematoxylin and eosin sections. Two nodes were positive on immunostained imprints and negative on haematoxylin and eosin-stained sections. One of these two nodes was the only sentinel node in one patient and was confirmed positive on immunostained paraffin sections. The other was found to be positive on haematoxylin and eosin-stained sections on reviewing the slide, but had been missed by the pathologist. Immunostaining of imprints missed one of two positive nodes in an axillary node clearance in the early part of the study because the node was not bisected correctly as described. The total number of positive nodes was 30 of 344.

On a patient basis, the sensitivities of IHC and haematoxylin and eosin staining were 100 and 88·9 per cent, and the NPV was 100 and 95·5 per cent, respectively. The 95 per cent confidence interval for the difference in proportions was − 0·065 to 0·134. On a node basis, sensitivities were 96·7 and 93·3 per cent and the NPV was 99·7 and 99·4 per cent for IHC and haematoxylin and eosin, respectively. The 95 per cent confidence interval for the difference in proportions was − 0·011 to 0·018. Because there were no false positives, the specificity and PPV were 100 per cent for both methods.

It was estimated that these results could be reported to the operating surgeon within 45 min of retrieval, depending on the number of sentinel nodes.

Discussion

Several different stains have been investigated for touch imprint cytology in evaluating SLNs intraoperatively. Quickdiff stain used by Turner *et al.*[18] resulted in an accuracy of 88 and 68 per cent, based on haematoxylin and eosin and IHC standards respectively. The Papanicolaou stain was used by Motomura *et al.*[7] with a sensitivity of 92·5 per cent, a specificity of 98·2 per cent and an overall accuracy of 96·7 per cent per node, and an overall accuracy of 96 per cent per patient. Haematoxylin and eosin was used by Ratanawichitrasin *et al.*[13] with a sensitivity of 93 per cent, a specificity of 100 per cent and overall accuracy of 98 per cent. It was also used by Rubio *et al.*[12] with an overall accuracy of 99·2 per cent, compared to that of haematoxylin and eosin sections.

Despite the routine use of immunostaining in tissue cultures and cellular smears, no specific protocol has been described previously for touch imprints from axillary nodes. Nevertheless, when the protocol of Richter *et al.*[19] for frozen sections was used on touch imprints, the results were not satisfactory. The protocol of rapid immunostaining of touch imprints used in the present study produced consistent and reproducible results.

The preliminary results using this protocol for the evaluation of axillary nodes during breast cancer surgery were concordant with those of permanent paraffin sections and were superior to the results of other staining methods. Interpreting the slides does not need an expert cytologist. The reporting of the results within 45 min of obtaining the node specimen is reasonable, as sentinel node biopsy often precedes mastectomy or wide local excision. These preliminary results suggest that IHC of touch imprints of axillary SLNs during surgery for breast cancer is feasible and could yield reliable results if done and interpreted carefully. The reproducibility and accuracy of this method need to be confirmed in large series.

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Effects of the combination of rapamycin with tacrolimus or cyclosporin on experimental intimal hyperplasia

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Background: Allograft vasculopathy remains the leading cause of late allograft failure following transplantation and can be inhibited by the antiproliferative drug rapamycin. This study assessed the efficacy of combining rapamycin therapy with calcineurin inhibition.
Methods: Male Sprague–Dawley rats received rapamycin 0·05 mg/kg daily and either tacrolimus 0·1 mg/kg or cyclosporin 5 mg/kg daily, and findings were compared with those in an untreated control group. Animals underwent left common carotid artery balloon angioplasty; the artery was explanted after 2 weeks. Morphometric analysis was performed on transverse sections and the intima : media ratio was calculated. Profibrotic gene expression was measured with competitive reverse transcriptase–polymerase chain reaction at 14 and 28 days. Proliferation was determined with proliferating cell nuclear antigen at 14 and 28 days. Extracellular matrix deposition was quantified with Sirius red.
Results: The combination of rapamycin and tacrolimus was associated with the greatest reduction in intimal thickening. Furthermore, treatment with rapamycin and tacrolimus significantly attenuated extracellular matrix deposition compared with rapamycin and cyclosporin ($P < 0.02$).
Conclusion: The effects of rapamycin in combination with tacrolimus were better than those observed with rapamycin and cyclosporin.

Paper accepted 13 July 2002

British Journal of Surgery 2002, **89**, 1390–1395

Introduction

Vascular narrowing, also known as allograft vasculopathy, is a central feature of the chronic rejection that occurs in all solid organ allografts[1,2]. Allograft vasculopathy is characterized histologically by intimal hyperplasia, a product of vascular smooth muscle cell proliferation, migration through the internal elastic lamina and deposition of extracellular matrix proteins[3].

The development of allograft vasculopathy is complex and dependent on multiple aetiological factors[4] including choice of immunosuppressive agents. Calcineurin inhibitors, such as cyclosporin and tacrolimus, form the mainstay of immunosuppressive regimens[5], but have failed to reduce the prevalence of allograft vasculopathy[6]. The novel macrolide rapamycin is also a potent immunosuppressive agent, but its antiproliferative effects extend beyond T-cell proliferation[7]. Recently Ikonen *et al.*[8] showed that administration of rapamycin halted the progression and also reversed established allograft vasculopathy in *Cynomolgus* monkeys.

Immunosuppressive regimens that reduce the prevalence of allograft vasculopathy offer a potential strategy for prolonging both graft and patient survival. In this study the effects of adding rapamycin to cyclosporin or tacrolimus therapy were investigated.

Materials and methods

Arterial injury model

Four-month-old male Sprague–Dawley rats (weighing 350–400 g) were obtained from Harland (Cambridge, UK) and cared for in accordance with the Animal (Scientific Procedures) Act 1986. Groups of six male rats received rapamycin 0·05 mg/kg daily and either tacrolimus 0·1 mg/kg or cyclosporin 5 mg/kg daily, and were compared with an untreated control group (six animals per group). Rats were anaesthetized with inhalational halothane and oxygen. The left common carotid artery was denuded of endothelium using a saline-filled 2-Fr balloon embolectomy catheter (Baxter Healthcare, Thetford, UK) as described previously[9]. Groups of rats were anaesthetized 14 and 28 days after balloon injury and the left common carotid artery was flushed with phosphate-buffered saline. The middle third of each vessel was used for histological and proliferation studies, and the outer thirds were snap-frozen in liquid nitrogen and stored at −70°C for molecular analysis.

Morphological study

Vessels for histological study were fixed with 2·5 per cent gluteraldehyde in 0·1 mol/l phosphate buffer (pH 7·4). After further fixation for 16 h, the vessels were embedded in epoxy resin and cut into 4-μm transverse sections. Intima and medial areas were calculated using light microscope-assisted computer planimetry. Intimal and medial areas were defined by internal and external elastic laminae respectively, and intimal thickening was expressed as the intima : media ratio.

Molecular analysis

Vessels were cut into 4-μm sections and messenger RNA was extracted using oligo-deoxythymidine-linked Dynabeads® (Dynal, Bromborough, UK). Competitive reverse transcriptase–polymerase chain reaction (RT-PCR) was performed as described previously[10]. Genes chosen for quantification included those of matrix metalloproteinase (MMP) 2 and MMP-9, tissue inhibitor of metalloproteinases (TIMP) 1, collagen III and transforming growth factor (TGF) β. All probes and primers were designed from sequences available on the EMBL database (European Molecular Biology Laboratories, Cambridge, UK) using the program GCG prime (Genetics Computer Group, Madison, Wisconsin, USA) and synthesized by Life Technologies (Paisley, UK) or Genosys Biotechnologies Europe (Pampisford, UK). Quantification of RT-PCR products was performed using an enzyme-linked immunosorbent assay. Differences in tissue cellularity were corrected for by expressing values of complementary DNA product as a ratio to that of the constitutively expressed housekeeping gene, β-actin.

Vascular smooth muscle cell proliferation studies

Specimens were cut into 4-μm sections and dried overnight on to 3-aminopropyltriethoxysilane-coated slides (Sigma, Poole, UK) at 37°C. Tonsillar tissue was used as a positive control. Before staining, sections were dewaxed in xylene and rehydrated through a series of graded alcohol solutions. Antigen retrieval was performed using preheated antigen-masking solution (Vector) in a microwave oven for 20 min. Proliferating cell nuclear antigen (PCNA) detection was performed as follows. Endogenous peroxidase was blocked by incubation with 3 per cent hydrogen peroxide for 30 min. Normal goat serum (Dako, Cambridge, UK) was then applied for 10 min, followed by mouse anti-PCNA (1 : 100; Dako) for 30 min. Antibody detection and amplification was achieved using biotinylated antimouse and a peroxidase-labelled streptavidin complex (Duet®; Dako). The enzyme complex was developed using 3-3′-diaminobenzidene to yield a brown reaction product. Sections were counterstained with haematoxylin before dehydration and mounting in DPX. Labelled and unlabelled cells, in both intimal and medial layers, were counted and the percentage of proliferating cells was calculated. Calculations were based on user-guided highlighting of cells using image analysis software (Lucia 4·81™; Laboratory Imaging Ltd, Minnesota, USA). For each sample, four pictures were taken under × 400 magnification, which represented the entire cross-section of the artery.

Sirius red staining

Carotid arteries were formalin-fixed, embedded in epoxy resin and cut into 4-μm sections. The resin was removed in xylene for 10 min and dehydrated in serial washes of 100 per cent alcohol for 2 min, performed twice, then in 95, 80 and 60 per cent alcohol for 2 min. Staining was carried out overnight for 12 h in picro–Sirius red F3BA (0·1 per cent Sirius red F3BA in saturated aqueous picric acid). Rapid dehydration was repeated with an initial wash of 0·01 mol/l hydrochloric acid for 2 min, and serial washes of 70 per cent alcohol for 45 s followed by 80, 95 and 100 per cent alcohol for 2 min. Slides were cleared with two washes of xylene for 2 min; excess xylene was removed and slides were mounted with Xam organic mountant. Four random windows of intima were analysed and the value for extracellular matrix was determined from the mean of these windows.

Statistical analysis

Student *t* test was used to determine statistical significance. $P \leq 0{\cdot}05$ was considered significant.

Results

Histological findings

There were significant differences in intimal thickening between all treatment groups after 14 days ($P < 0{\cdot}006$, Kruskal–Wallis test), and a marginal reduction after 28 days ($P < 0{\cdot}08$). Rapamycin in combination with tacro-

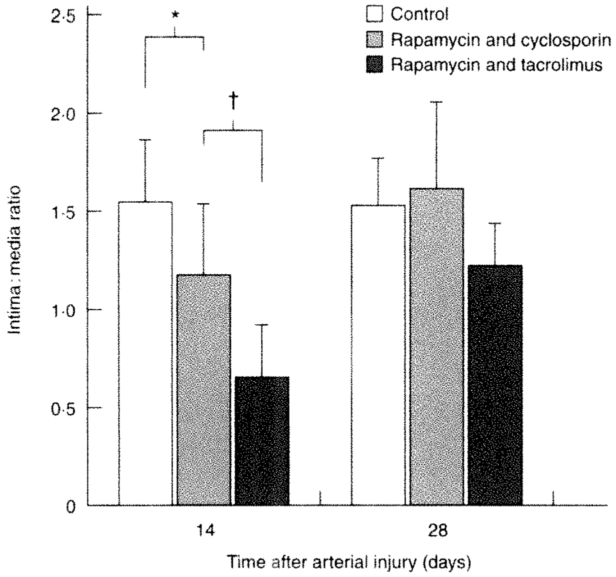

Fig. 1 Effect of rapamycin in combination with cyclosporin or tacrolimus on intima : media ratio 14 and 28 days after arterial balloon injury. Values are mean with standard error. $^{*}P < 0\cdot003$, $\dagger P < 0\cdot03$ (Student *t* test)

Table 1 Effect of treatment with rapamycin and either cyclosporin or tacrolimus on profibrotic gene expression

Gene	Control	Rapamycin and cyclosporin	Rapamycin and tacrolimus
MMP-2			
14 days	2·41 (1·88–3·62)	0·87 (0·62–1·04)*	1·02 (0·79–1·27)*
28 days	1·32 (1·09–1·68)	0·70 (0·58–0·89)*	0·68 (0·42–0·99)*
MMP-9			
14 days	1·40 (0·96–1·93)	0·46 (0·37–0·68)*	0·51 (0·42–0·70)*
28 days	0·54 (0·37–0·82)	0·49 (0·39–0·62)	0·47 (0·43–0·67)
TIMP-1			
14 days	1·61 (1·11–2·09)	0·82 (0·73–0·96)*	0·94 (0·63–1·26)*
28 days	0·98 (0·59–1·37)	0·78 (0·66–0·86)*	0·80 (0·57–0·98)
TGF-β			
14 days	1·87 (1·68–3·05)	0·64 (0·53–0·75)*	0·72 (0·46–1·00)*
28 days	1·23 (0·97–1·61)	0·65 (0·49–0·72)*	0·67 (0·53–0·74)*
Collagen III			
14 days	1·51 (1·01–2·32)	0·56 (0·43–0·69)*	0·61 (0·48–0·87)*
28 days	0·88 (0·67–1·05)	0·52 (0·39–0·67)*	0·49 (0·31–0·76)*

Values are mean (range). MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; TGF, transforming growth factor. There were no significant differences between the two treatment regimens. $^{*}P < 0\cdot05$ *versus* controls (analysis of variance)

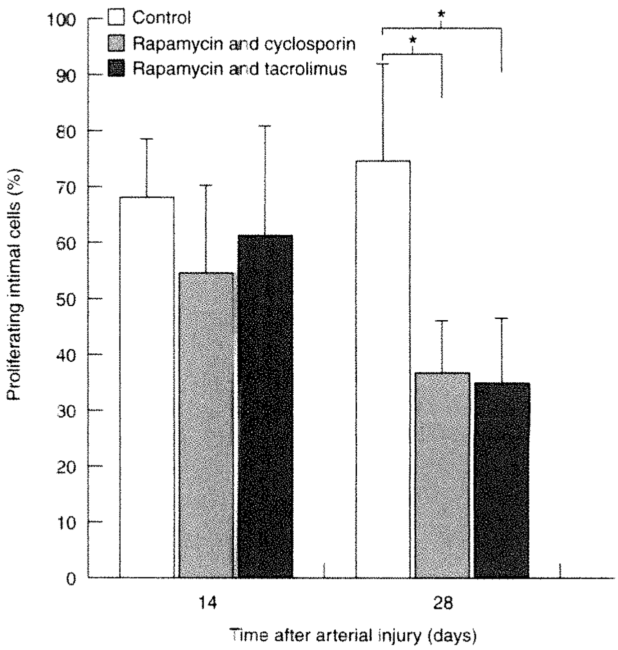

Fig. 2 Effect of rapamycin in combination with cyclosporin or tacrolimus on intimal vascular smooth muscle cell proliferation after balloon angioplasty. Values are mean with standard error. $^{*}P < 0\cdot001$ (Student *t* test)

limus, but not with cyclosporin, inhibited intimal thickening at 14 days compared with untreated controls ($P < 0\cdot003$) (*Fig. 1*). Furthermore, rapamycin with tacrolimus significantly reduced intimal thickening compared with rapamycin with cyclosporin ($P < 0\cdot03$). However, rapamycin and tacrolimus resulted in a non-significant reduction in intimal thickening at 28 days compared with its combination with tacrolimus and untreated controls ($P < 0\cdot07$ for both groups).

Profibrotic gene expression

Rapamycin in combination with both cyclosporin and tacrolimus significantly inhibited the expression of MMP-2, TGF-β and collagen III at both 14 and 28 days ($P < 0\cdot01$ for all genes at 14 and 28 days) (*Table 1*). Both treatment groups significantly inhibited MMP-9 and TIMP-1 at 14 days ($P < 0\cdot006$), but only cylcosporin and rapamycin inhibited TIMP-1 at 28 days. There were no significant differences in profibrotic gene expression between treatment groups for each gene studied at either time-point.

Proliferation studies

In both treatment groups intimal proliferation after 28 days was inhibited ($P < 0\cdot001$, Student *t* test), but there was no effect at 14 days compared with controls (*Fig. 2*). Medial smooth muscle cell proliferation at 14 days was inhibited by rapamycin with tacrolimus ($P < 0\cdot04$) but not by the combination with cyclosporin (*Fig. 3*). While there was no difference between control animals and those treated

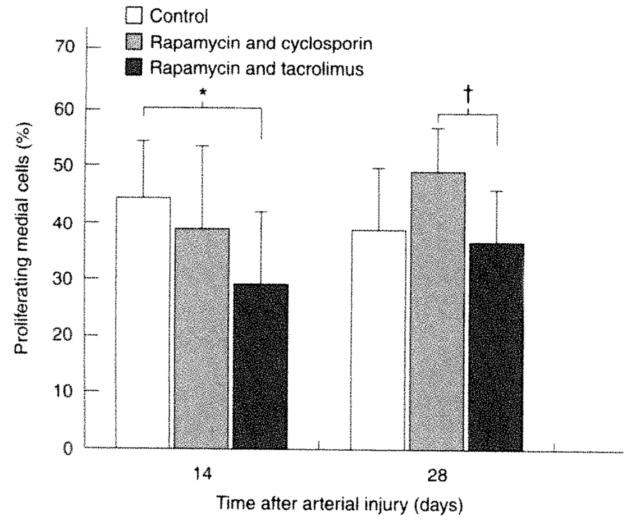

Fig. 3 Effect of rapamycin in combination with cyclosporin or tacrolimus on medial vascular smooth muscle cell proliferation after balloon angioplasty. Values are mean with standard error. *$P < 0.04$, †$P < 0.008$ (Student *t* test)

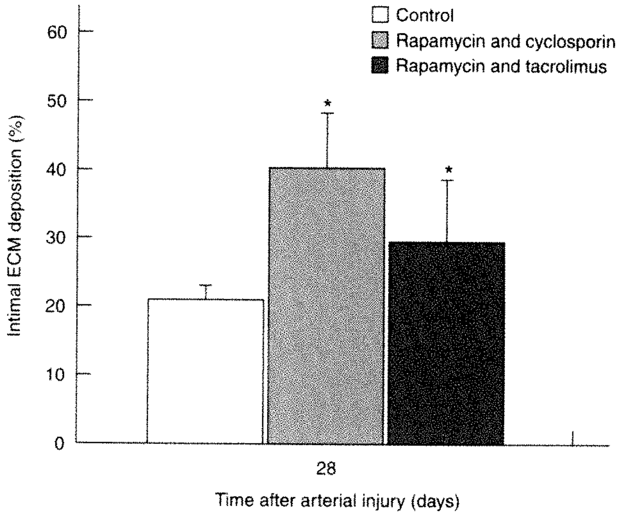

Fig. 4 Effect of rapamycin in combination with tacrolimus or cyclosporin on intimal extracellular matrix (ECM) deposition 28 days after balloon angioplasty. Values are mean(s.e.m.). *$P < 0.02$ *versus* control (Student *t* test)

with rapamycin and cyclosporin, the combination of rapamycin and tacrolimus significantly reduced intimal proliferation at 28 days compared with that observed following treatment with rapamycin and cyclosporin ($P < 0.008$).

Extracellular matrix deposition

Intimal extracellular matrix deposition was increased by treatment with rapamycin and both tacrolimus and cyclosporin ($P < 0.015$, Student *t* test) (*Fig. 4*). Treatment with rapamycin and cyclosporin significantly increased the accumulation of extracellular matrix proteins compared with controls ($P < 0.008$). However, treatment with rapamycin and tacrolimus showed no increase in extracellular matrix deposition and was associated with a marginal reduction in intimal extracellular matrix deposition compared with the cyclosporin group ($P < 0.02$).

Discussion

The introduction of cyclosporin has dramatically improved short-term survival rates following heart transplantation[11], but has failed to reduce the incidence of chronic rejection, more accurately known as cardiac allograft vasculopathy (CAV). Tacrolimus, another calcineurin inhibitor, is a potent immunosuppressive agent that has reduced the rate of acute rejection following cardiac transplantation[12,13]. However, experimental studies have suggested that tacrolimus may accelerate rather than inhibit the development of CAV[14,15]. These deleterious findings may be attributed to the side-effects of calcineurin inhibitors, which include hypertension, hyperlipidaemia and glucose intolerance[16]. The present study investigated the addition of the novel immunosuppressive and antiproliferative agent, rapamycin, to calcineurin inhibitors in a model of intimal hyperplasia, independent of their immunosuppressive properties.

The study showed that rapamycin in combination with either cyclosporin or tacrolimus significantly inhibited early intimal thickening, but only its prolonged administration with tacrolimus showed a marginal reduction in intimal thickening compared with untreated controls or cyclosporin. These findings were supported by the proliferation studies. Following vascular injury, medial vascular smooth muscle cells began proliferating and migrated through the internal elastic lamina to form a neointima. The intimal lesion increased in size by further intimal proliferation and the deposition of extracellular matrix proteins. In the present study, only treatment with rapamycin and tacrolimus significantly inhibited early medial smooth muscle cell proliferation, whereas the combination of rapamycin and cyclosporin increased late medial smooth muscle cell proliferation compared with controls. Neither treatment regimen had an effect on early intimal proliferation but both treatments inhibited late intimal proliferation in comparison with untreated controls. In summary, these findings suggest that treatment with rapamycin and tacrolimus inhibited the early medial smooth muscle cell response following injury, whereas both treatments inhibited late intimal proliferation, suggesting the potential to inhibit the progressive nature of allograft vasculopathy[17].

Treatment with rapamycin and both cyclosporin and tacrolimus significantly inhibited profibrotic gene expression compared with controls. Following vascular injury, medial vascular smooth muscle cells increased expression of zinc-containing endopeptidases known as MMPs. These proteases have specific substrates, but together are capable of degrading all the components of the extracellular matrix[18]. Furthermore, MMP-2 and MMP-9 are also pivotal mediators of vascular smooth muscle cell proliferation and migration[19]. MMP-2 is expressed constitutively but its expression, like that of MMP-9, is induced after injury[20,21]. Proliferating medial vascular smooth muscle cells must digest the surrounding extracellular proteins to migrate across the internal elastic lamina. Increased expression of MMP-2 and MMP-9 facilitates this process[22], whereas an increase in their naturally occurring TIMPs is inhibitory[23].

Both treatment groups had significantly inhibited MMP-2 and MMP-9 expression after 14 days, which may have accounted for the observed reduction in early medial smooth muscle cell proliferation seen in the tacrolimus group. Expression of collagen III and TGF-β was inhibited significantly by both treatment groups at early and late time-points. Conversely, both groups demonstrated an increase in extracellular matrix deposition compared with controls. However, Sirius red is not selective for collagen III, but stains for all components of the extracellular matrix[24] and, while collagen III is a major component of the intimal lesion[25], it was the only extracellular matrix protein assessed in this study.

Multiple-agent regimens are advocated to increase immunosuppression in comparison with monotherapy, while minimizing toxic side-effects. The long-term effectiveness of both cyclosporin and tacrolimus is limited by adverse effects. Potential additive or synergistic interactions between different groups of immunosuppressive agents may allow lower doses to be used, thus minimizing side-effects and potentially improving long-term graft survival. Vu *et al.*[26] previously demonstrated that rapamycin and tacrolimus extended graft survival following cardiac transplantation in the rat compared with monotherapy. These findings are supported by earlier studies of Morris *et al.*[27].

The present study suggests that the combination of rapamycin and tacrolimus is associated with a greater reduction in vascular narrowing, smooth muscle cell proliferation and accumulation of extracellular matrix proteins compared with the combination of rapamycin and cyclosporin. Further studies are warranted to assess whether tacrolimus should be the primary calcineurin inhibitor of choice when used in combination with rapamycin.

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Cryotherapeutic ablation of liver tumours

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Background: This paper reports a 7-year experience of cryoablation for colorectal and non-colorectal liver metastases.

Methods: A retrospective review was undertaken of patients treated in two adjacent UK centres in the north-west of England.

Results: Over a 7-year period (1993–2000), 57 patients underwent cryotherapy for malignant hepatic tumours (41 colorectal, 16 non-colorectal). In the patients with colorectal metastases, preoperative carcinoembryonic antigen (CEA) levels fell significantly, from a mean of 444·1 to 6·22 μg/l ($P = 0{\cdot}002$). One patient died, two developed cryoshock and six had cardiorespiratory complications. All patients with colorectal metastases subsequently received 5-fluorouracil-based chemotherapy. The remaining 16 patients with non-colorectal tumours (seven neuroendocrine metastases, five hepatocellular carcinomas, three sarcomas, one cholangiocarcinoma) all received cryotherapy alone, with no major complications. The median survival for patients with non-colorectal metastases was 37 months, compared with 22 months for those with colorectal metastases ($P = 0{\cdot}005$).

Conclusion: Hepatic cryotherapy is effective and safe, as demonstrated by the significant reduction in postoperative CEA concentration and the low risk of complications. However, this initial short-term success was not reflected in 5-year survival rates. Cryotherapy for non-colorectal metastases had a greater long-term survival benefit and is a useful means of controlling symptoms.

Paper accepted 5 August 2002

British Journal of Surgery 2002, **89**, 1396–1401

Introduction

Almost 30 000 new cases of colorectal cancer are diagnosed each year in the UK[1]. The liver is the most common site for metastases[2], detected synchronously with the primary tumour in 25 per cent of patients and metachronously in a further 40 per cent[3]. Overall, half of all patients with colorectal cancer will develop liver metastases, but only 5–10 per cent of these will be resectable[3].

Surgical resection is now widely accepted as the treatment of choice for patients with four or fewer metastases, with series from around the world reporting 5-year survival rates of between 20 and 50 per cent[4–7]. However, for the majority of patients with colorectal cancer, better treatments are required to complement the existing range of chemotherapeutic regimens.

Cryotherapy for primary and secondary malignant liver tumours has been reported to be effective, compared with best supportive care[2–7]. It is of particular value in cases where resection is difficult because of proximity of vessels, extensive infiltration or cirrhosis, and has been advocated in some centres as an alternative to resection[8].

This paper reports the experience from two adjacent tertiary referral centres in the UK. Patients were selected sequentially by clinical need between October 1993 and October 2000, and the results were assessed retrospectively.

Patients and methods

Between October 1993 and October 2000, 57 patients underwent cryotherapy for primary or secondary, histologically or biochemically confirmed, malignant liver tumours. Thirty-six patients were male and 21 were female, with a median age of 58 (range 17–83) years. Forty-one patients (72 per cent) had colorectal liver metastases. The metastases in 15 of these patients were detected synchronously with the primary tumour and the other 26 were detected metachronously. Of the metachronous metastases, 18 were Dukes' C lesions, seven were Dukes' B and one was Dukes' A.

Cryotherapy was performed in three clinical scenarios. In group 1 (21 patients), cryotherapy was used to provide ablative therapy in patients deemed unsuitable for liver resection on either radiological or laparotomy findings. In most cases the intention to treat was 'curative'. In group 2 (17 patients), cryotherapy was used to complement a liver resection. The cryotherapy was used with a 'curative' intention to ablate a residual metastasis not included in the initial surgical resection, for example in the contralateral lobe. In group 3 (three patients), cryotherapeutic ablation was used as a 'palliative' treatment in cases where unexpected extrahepatic disease was found at the time of staging laparotomy, which precluded a surgical resection.

During the study period, 417 liver resections were performed in patients with colorectal cancer and 100 resections for non-colorectal liver tumours. Patients who received cryotherapy represented only 10 per cent of those undergoing resection, and only 4 per cent of the total had combined therapy.

Computed tomography (CT) of the chest and abdomen was performed before operation to stage all patients. All data relating to the findings on initial laparotomy, operation or procedure performed, blood investigations carried out before and after operation (liver function tests, haemoglobin and international normalization ratio (INR)), postoperative complications and survival outcomes were collected retrospectively.

At laparotomy, a careful assessment of intra-abdominal disease was made by means of intraoperative ultrasonography (5–7-MHz medical ultrasound scanner type 2002 AD 1; B & K Medical, White Waltham, UK). Cryotherapy was administered by the Liquid Cryo system 2000 (Spembly Medical, Andover, UK) and was monitored by intraoperative ultrasonography. The cryoprobes used were either 10- or 3-mm needle trocars, or a 40-mm flat trocar (CE0086; Spembly Medical), depending on the size or depth of the lesion. Probes were positioned by a combination of palpation and ultrasonographic guidance. After cryotherapy, the probe cavity was packed with Surgicel® (Ethicon-SARL, Runcorn, UK) and the surface sutured to ensure haemostasis.

Most metastases underwent only one cycle of freezing. The size of the ice-ball was ensured to extend at least 1 cm beyond the edge of the tumour in all directions by ultrasonographic control. In two patients in group 1 with multiple large deposits, only the largest lesions were treated because of concern over the volume of tissue frozen, but in the remaining patients all lesions were treated at one procedure. For lesions greater than 5 cm in diameter, two cryoprobes were inserted simultaneously to ensure adequate ice-ball size. This was combined with temporary portal inflow occlusion for lesions with a diameter of 10 cm or more.

All data were analysed for patient demographics and disease-free survival time from operation until recurrence in the liver. Follow-up CT was performed at 6 weeks and then every 6 months until death. Overall survival, using Kaplan–Meier analysis, from the time of operation until death was compared between patients with non-colorectal and those with colorectal metastases. Statistical significance was determined with the log rank test. Differences between the two groups were compared in terms of median survival, length of disease-free survival (months) and 5-year survival rate. Statistical significance of any difference in the mean preoperative and postoperative serum carcinoembryonic antigen (CEA) levels (μg/l) compared to a normal value of 5 μg/l were determined by the McNemar test.

Results

Colorectal metastases

Forty-one patients received cryotherapy for colorectal metastases. The median follow-up was 19 (range 1–66) months. One patient died in hospital from postoperative myocardial infarction. Two patients developed the symptoms and signs of cryoshock, but both responded to supportive treatment and recovered. One of these patients, from group 1, had two large lesions (3·5 and 10 cm) and received cryotherapy for a total of 80 min. The second patient, from group 2, had cryotherapy for 47 min after initial resection. However, two other patients received cryotherapy for 100 and 200 min without developing any sign of cryoshock. In group 1, two patients developed symptomatic right-sided pleural effusions, both had tumours in the right lobe, which were close to the dome of the diaphragm. One further patient in group 2, who underwent liver resection with 4 min of cryotherapy to the edge of the resection margin, exhibited signs of acute liver failure, which recovered. A further six serious postoperative complications were all due to cardiorespiratory problems. All patients received 5-fluorouracil-based chemotherapy for 6 months, commencing within 6 weeks of ablation.

Patients in group 1 had a median survival of 25 months; three of the 21 patients were still alive at 27, 43 and 71 months. One patient in group 1 received cryotherapy totalling 65 min to 11 lesions and is alive after 60 months. Two patients in group 1 received cryotherapy only to the largest lesions, leaving smaller metastases untreated, and therefore cannot be considered to have been treated with 'curative' intent. These two patients survived for a further 19 and 13 months, with no serious complications. Patients in group 2 had a similar median survival of 23 months, with three of the 17 patients still alive at 9, 43 and 54 months. The median survival of the three patients in group 3 was significantly shorter than that of the other two groups, at only 11 months, with one patient surviving for 26 months.

The overall median survival for all three groups was 22 months; six patients were still alive at the time of analysis (March 2001) (*Fig. 1*). Using Kaplan–Meier analysis of all patients with colorectal metastases, at 3 and 5 years 14 and five patients were alive, respectively (*Table 1*, *Fig. 1*); the median disease-free survival was 12 months. Twenty-six of the 41 patients developed recurrence: two had bone metastases, one was found to have lung metastases, and the remaining 23 recurrences occurred in the liver remnant, of which only five developed at the cryosite.

Non-colorectal metastases

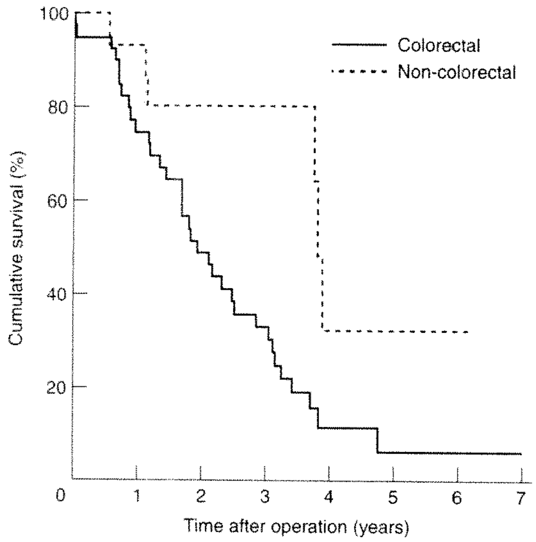
Sixteen patients with non-colorectal metastases were treated with cryotherapy: seven had metastatic neuroendocrine tumours, five had hepatocellular carcinoma (HCC), three had metastatic sarcoma and one cholangiocarcinoma. The median follow-up of these patients was 30 (range 12–60) months.

Medical control of endocrine symptoms had failed in all of the patients with neuroendocrine tumours. Six had the carcinoid syndrome, and the remaining patient had a metastatic insulinoma. The indication for ablation was to improve the endocrine symptoms by debulking the tumour volume. The median survival for these patients from time of operation was 28 months; all patients were still alive with recurrent disease. The overall median disease-free survival for this group was 9 months. Recurrence occurred in the liver remnant in four patients and at extrahepatic sites in the remaining two, with the development of omental thickening and ascites in one patient. In all cases the endocrine symptoms were clinically improved and medical therapy was reduced, and in some cases stopped completely for up to 6 months.

All the HCCs treated (size range 2·5–5 cm) arose in cirrhotic livers. The median survival for these patients after treatment was 36 months, with a disease-free survival of only 7 months. Two patients were still alive at 36 and 44 months. The latter patient also received transarterial chemoembolization for recurrences, with good outcome.

The metastatic sarcomas that were treated included a malignant fibrous histiocytoma, a liposarcoma and a gastrointestinal stromal tumour. Two patients were alive, with recurrence, at 29 and 66 months. The median survival was 36 months, with a median disease-free survival of only 8 months. The patient with cholangiocarcinoma survived for 46 months after cryotherapy. The overall median survival for patients with non-colorectal metastases was 37 months, and ten of the 16 patients were still alive at the time of analysis (*Fig. 1*). The overall survival rate of all patients with non-colorectal metastases at 3 and 5 years was 80 and 32 per cent respectively (*Table 1*, *Fig. 1*).

There were no 30-day postoperative deaths in these patients, and only two patients had morbidity as a result of transient ischaemic attacks, from which both recovered. Patients with non-colorectal liver metastases benefited from significantly better 3- and 5-year survival rates after treatment than those with colorectal metastases (*Fig. 1*, *Table 1*) (P = 0·005, log rank test). Median overall survival for patients with non-colorectal metastases (37 months) was better than that for patients with colorectal metastases (22 months) (P = 0·005, log rank test).



No. at risk								
Colorectal	41	36	33	20	7	3	2	1
Non-colorectal	16	15	15	12	11	9	3	2

Fig. 1 Cumulative survival following cryotherapy of colorectal and non-colorectal metastases. P = 0·005 (log rank test)

Table 1 Overall survival of patients with colorectal and non-colorectal metastases undergoing cryotherapy

	Survival	
	3 years	5 years
Colorectal metastases	14	5
Non-colorectal metastases	12	8*

*P = 0·005 *versus* colorectal metastases (log rank test)

Blood biochemistry

Postoperative blood tests were performed daily for 5 days. These demonstrated a massive rise (16 times above the normal range) in both serum aspartate aminotransferase and alanine aminotransferase in patients with colorectal or non-colorectal metastases. This is in line with the findings of other studies and simply reflects the damage done to liver cells by the ablation technique.

Blood haematology

Blood haemoglobin levels did not fall by more than 2 g/dl in either group of patients after treatment. Similarly, the INR was not significantly affected by cryosurgery. Fifteen patients with colorectal metastases required a blood transfusion (mean(s.e.m.) 4·6(2·8) units). Only two patients had more than 10 units of blood transfused during the hospital stay, and there were no major complications directly associated with excessive bleeding that needed relaparotomy for uncontrolled bleeding.

Carcinoembryonic antigen

After cryosurgery, serum CEA levels fell in all patients with colorectal metastases, from a mean preoperative level of 444·1 μg/l to a mean postoperative level of 6·22 μg/l (normal range 0–5 μg/l) ($P = 0{\cdot}002$, McNemar test).

Discussion

The long-term 5-year survival rate following hepatic cryotherapy was disappointing, but probably reflects the real practical experience of two tertiary referral centres. The 5-year survival rate for colorectal metastases (five patients), although not a randomized comparison, was not greatly different from that obtained with modern chemotherapy regimens[9] and compares poorly with results from resection performed in these two centres over the same time-scale (36 per cent for 417 resections), which is well within the accepted range[4,7]. Furthermore, the use of open surgery may have resulted in more accurate staging of disease than a laparoscopic or percutaneous approach[5,10,11].

The significant fall in mean postoperative serum CEA concentration, from 444·1 to 6·2 μg/l, attests to the success of the technique in ablating liver colorectal metastases in this series and providing good short-term local control, as confirmed by follow-up radiological examination, and compares well with other reports[5,6]. Equally, the significant changes in liver enzyme concentrations reflect the success of the ablation therapy.

Arnott[12] initially described the use of freezing to treat cancer more than 150 years ago. Cold temperatures achieve cell death by the formation of intracellular ice crystals[13,14], which lead to rupture of the cell membrane and 64–82 per cent cell death[5]. Modern cryotherapy equipment employs the use of a closed triple-lumen probe[5], the highly conductive tip reaching temperatures of −196°C, inducing necrosis as well as microvascular damage and resulting in hypoxic cell death[13,15]. The rapid freeze–thaw process enhances necrosis and is purported to induce an autoimmune response against the surviving tumour cells[16]. After 2–3 days the dead tissue is converted to a fibrous scar[17]. As in this series, the use of cryosurgery may be enhanced under intraoperative ultrasonographic guidance[15], and most authors advocate that the ice-ball should extend 1 cm beyond the lesion to achieve complete cryodestruction of the tumour[18].

The results from this series of patients treated with cryoablation of colorectal cancer liver metastases mirror data from around the world in terms of reduction in CEA levels[2,15,18] and median survival (reported range 19–32 months)[19], but only a few centres have reported 5-year survival data[20]. Although no prospective randomized trial has compared cryoablation with liver resection for potentially resectable liver tumours, Korpan[20] has described a randomized clinical trial that compared a special cryogenic clamp favourably with resection.

The poor 5-year survival rate found in the present study could be explained by variations in technique, such as the use of single and double freeze–thaw cycles, selective use of portal inflow occlusion, and the choice of which lesions were too big or too numerous for ablation.

Two-cycle cryotherapy has been advocated[10,15] and may improve long-term survival[6]. This series employed one-cycle freezing in the majority of patients, unless the lesion was inadequately covered by the ice-ball, and this may have been a reason for failure on some occasions. Two-cycle freezing significantly increased total operating time.

Portal inflow occlusion was used selectively in this series only in lesions larger than 10 cm and was found not to be necessary for smaller lesions, which froze rapidly. The proximity of blood vessels, with their inherent warming effect, may render cryotherapy ineffective[15]. Cautious portal inflow occlusion prevents this rewarming from the blood flow[5], but increases the risk of vessel wall necrosis and subsequent intratumoral or extrahepatic bleeding[15,17].

This series included tumours greater than 6 cm, whereas better survival has been reported with ablation of lesions smaller than 3 cm[18,21]. The risk of cryoshock, a syndrome manifested by varying degrees of acute renal failure, disseminated intravascular coagulation and adult respiratory distress syndrome[16,22], was not directly related to lesion size in this series. Cryoshock is reported to be proportional to the volume of tissue treated (greater than 40 per cent)[13], and lesions over 6 cm are associated with a greater risk[18]. However, lesions up to 10 cm in size were treated safely. This phenomenon may be related more to the total duration of cryotherapy than to the volume of tumour treated. Two patients who experienced cryoshock had a protracted duration of cryotherapy (80 and 47 min).

Similarly, up to 11 lesions in a patient were treated, and others have reported successful treatment of up to 15 lesions in a single patient[22]. The patient with 11 lesions treated (group 1) had a total of 65 min of cryotherapy with no adverse complications, and was alive 60 months after treatment.

There was no significant difference in survival following treatment between patients in group 1 (cryotherapy only; median survival 25 months) and those in group 2 (resection and cryotherapy; median survival 23 months), although the numbers were relatively small. Patients who were treated in the presence of extrahepatic disease survived for a median of 11 months, which is little or no better than palliative systemic chemotherapy, although one patient did survive for 26 months after treatment. It is concluded that there is little or no benefit for ablation of colorectal liver metastases in the presence of extrahepatic disease. This confirms the value of open *versus* laparoscopic or percutaneous methods[11], which may not have the benefit of accurate disease staging afforded by open laparotomy.

For non-colorectal malignant liver tumours treated by cryosurgery, Zhou *et al.*[23] have demonstrated a 5-year survival rate of 49 per cent for irresectable HCC smaller than 5 cm in diameter. In the present series the median size of treated HCCs was 4 (range 2·5–5) cm, with a median survival of 36 months. Two patients were still alive at 36 and 44 months. HCC appears to respond better to cryotherapy than metastases from colorectal cancer[8,24] and is a useful treatment modality for patients with HCC, in whom cirrhosis often precludes surgery[22].

Cryotherapy also appears to be extremely useful and safe in the treatment of irresectable neuroendocrine metastases, combining control of endocrine symptoms with some degree of tumour regression[21], and improves survival[10]. All seven patients with neuroendocrine metastases were still alive at the time of reporting, with an overall median survival of 28 months. Cryotherapy for neuroendocrine metastases offers a useful additional treatment modality to be combined with resection and hepatic artery embolization according to individual circumstances[21,25].

Apart from cryoshock, the other serious complication of cryotherapy is haemorrhage, which usually occurs with a concomitant clotting disorder including a low platelet count and change in INR and partial thromboplastin time[2–8,22]. This was not an appreciable risk in the present study, with little change in the preoperative and postoperative INR and little bleeding overall. Other, more minor, reported complications include liver abscess (not seen in this study) and pleural effusion (seen in two patients), which appears to be more common when lesions are treated near the dome of the right diaphragm[16,22,26].

Liver resection remains the treatment of choice for colorectal metastases and primary liver tumour. Cryotherapeutic ablation provided a disappointing 5-year survival rate, although the initial short-term response and survival appeared promising during follow-up. In part, this may have been due to this group of patients inherently having a worse prognosis as a direct consequence of the greater extent of disease. Variations in the cryotherapeutic technique that could be relevant include the number of freeze cycles used and the use of portal inflow occlusion.

These results urge caution regarding the initially good short-term results following ablation techniques. In a field where there is much patient variation, disease variation and technique variation, it is essential that all ablative techniques be evaluated in randomized controlled trials before gaining widespread (and possibly unjustified) acceptance.

Acknowledgements

The authors thank Mrs Elizabeth Gardener, Department of Research and Development, North Manchester General Hospital (NMGH), for help with the statistical analyses, and Mrs Deborah Dunton and staff at the Postgraduate Centre for Education, NMGH, for help with the literature review. All the work was supported by Help Against Liver Tumours (HALT) (registered charity no. 1054556), which is based at NMGH.

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Association of Surgeons

Emergency surgeon-performed hepatobiliary ultrasonography

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Background: Acute hepatobiliary pathology is a common general surgical emergency referral. Diagnosis requires imaging of the biliary tree by ultrasonography. The accuracy and impact of surgeon-performed ultrasonography (SUS) on the diagnosis of emergent hepatobiliary pathology was examined.

Methods: A prospective study, over a 6-month period, enrolled all patients with symptoms or signs of acute hepatobiliary pathology. Patients provided informed consent and underwent both SUS and standard radiology-performed ultrasonography (RUS). SUS was performed using a 2–5-MHz broadband portable ultrasound probe by two surgeons trained in ultrasonography, and RUS using a 2–5-MHz fixed unit. SUS results were correlated with those of RUS and pathological diagnoses.

Results: Fifty-three consecutive patients underwent 106 ultrasonographic investigations. SUS agreed with RUS in 50 (94·3 per cent) of 53 patients. SUS accurately detected cholelithiasis in all but two cases and no patient was inaccurately diagnosed as having cholelithiasis at SUS (95·2 per cent sensitivity and 100 per cent specificity). As an overall complementary diagnostic tool SUS provided the correct diagnosis in 96·2 per cent of patients. Time to scan was significantly shorter following SUS (3·1 *versus* 12·0 h, $P < 0.05$).

Conclusion: SUS provides a rapid and accurate diagnosis of emergency hepatobiliary pathology and may contribute to the emergency management of hepatobiliary disease.

Paper accepted 30 August 2002

British Journal of Surgery 2002, **89**, 1402–1404

Introduction

Cholelithiasis is present in up to 10 per cent of the population and as a consequence acute biliary disease is a common cause for emergency hospital admission[1]. The accurate diagnosis of the pathological aetiology relies on ultrasonographic imaging of the hepatobiliary tree to define the liver, biliary apparatus and pancreas[2]. While the pancreas may be inaccessible to ultrasound owing to its deep position behind the upper gastrointestinal tract, the liver, gallbladder and biliary tree are generally easily visualized ultrasonographically.

Medical ultrasonography utilizes high-frequency sound waves, produced from electrical energy by a piezoelectric element. These ultrasound waves are transmitted to tissues, reflected by tissues of differing acoustic impedance and then interpreted, following the conversion back from sound to electrical energy, as an image on the ultrasound output monitor. Recent technological advances have produced small portable ultrasound machines with high-frequency broadband ultrasound transducers, which can readily be taken to the patient rather than the patient having to attend a specific department for ultrasonogaphy. It remains unclear who may be best trained and qualified to use the equipment[3–5]; although traditionally ultrasonography has been performed by radiologists, it has been suggested that it may be used successfully by surgeons following appropriate training[6,7].

In the UK and Ireland, no guidelines exist for the training of surgeons in the use of ultrasonography. This study examined the use of ultrasonography in diagnosing acute hepatobiliary pathology because this is a common surgical problem and there are clear sonographic criteria for diagnosis. The results of surgeon-performed ultrasonography (SUS) have been compared with those obtained following standard care pathways for patients presenting with acute hepatobiliary pathology.

Patients and methods

Over a 6-month period all patients referred for emergency surgical review with symptoms or signs of suspected hepatobiliary pathology were considered for entry into the study. Symptoms were either suggestive of biliary colic or right upper quadrant pain with clinical signs to support the diagnosis of hepatobiliary pathology. After review by the surgical team appropriate patients were entered into the study and timepoints taken henceforth.

Patients gave informed consent to undergo SUS in addition to standard care. SUS was performed using a portable ultrasound machine with a 2–5-MHz curved broadband transducer (Sonosite, Bothell, Washington, USA) in accordance with a local ethics committee-approved protocol. Simultaneously, emergency ultrasonography was also requested as part of the standard care plan from the radiology department. Radiology-performed ultrasonography (RUS) was performed again using a 2–5-MHz broadband transducer with a base ultrasound unit (GE Medical Systems, Hino, Japan). RUS was interpreted by a radiology trainee and checked by a consultant radiologist. Radiologists performing RUS were unaware of the results of SUS. Time to scan was measured as the time from study entry to the scan being performed.

Two surgical trainees trained in ultrasonography performed SUS. Training involved a 5-day course comprising 25 h of American Medical Association Category I credit (Jefferson Ultrasound Research and Education Institute, Philadelphia, Pennsylvania, USA). For all patients final data on patient demographics were taken from discharge profiles and the final diagnosis from histopathological samples. For cholelithiasis, this was the final diagnosis following operative treatment.

Patients were fasted for 6 h before imaging. The sonographic criterion for stone recognition was a mobile hyperechoic focus with posterior shadowing seen within the gallbladder. Sonographic criteria for acute cholecystitis were gallbladder wall thickness greater than 3 mm in the fasting state, sonographic Murphy's sign, fluid in the pericholecystic space and oedema with shedding of the gallbladder mucosa seen as lines within the gallbladder. Biliary dilatation was diagnosed when the common bile duct diameter was more than 8 mm and intrahepatic biliary dilatation was confirmed if the bile ducts could be visualized running parallel with the portal veins within the liver.

Data were analysed using the Statistical Package for the Social Sciences version 10 (SPSS®, Chicago, Illinois, USA). Descriptive statistics were used for comparative analysis and Student's *t* test for parametric data.

Results

Over 6 months, 53 patients were recruited, with a mean age of 48 (range 14–86) years and a male : female ratio of 1 : 2·6. SUS agreed with RUS in all but three of the 53 patients. In two of these three patients, gallstones were not seen at SUS. Both of these patients presented with biliary obstruction demonstrated at SUS, although the cause was not identified. The range of pathologies diagnosed is shown in *Table 1*.

Table 1 Final diagnosis at discharge

Diagnosis	No. of patients
Pancreatitis	2 (3·8)
Gastritis	4 (7·5)
Acute cholecystitis	10 (18·9)
Biliary colic	28 (52·8)
Obstructive jaundice	6 (11·3)
Liver metastasis	1 (1·9)
Cirrhosis	1 (1·9)
Gallbladder sludge	1 (1·9)
Total	53 (100)

Values in parentheses are percentages

Forty-two of the 53 patients had gallstones. Of these 42, gallstones were identified accurately at SUS in 40 and at RUS in 41 patients. One patient thought not to have cholelithiasis at RUS was thought to have sludge and cholelithiasis at SUS. At repeat RUS, cholelithiasis was confirmed. All patients presenting with gallstones without jaundice were diagnosed accurately with SUS. The sensitivity and specificity for the diagnosis of cholelithiasis in patients presenting acutely were 95·2 and 100 per cent respectively. SUS gave a positive predictive value (PPV) of 100 per cent and a negative predictive value (NPV) of 84·6 per cent for the detection of cholelithiasis. To assess the impact of SUS, the ultrasonographic diagnosis was compared with the final diagnosis. A SUS diagnosis was made after the initial surgical assessment and SUS. SUS was accurate in 51 of 53 patients. Both incorrect diagnoses were thought to be malignant biliary obstruction at the level of the pancreas, but in both cases common bile duct stones were seen at RUS. This gave SUS an overall sensitivity of 95·2 per cent and a specificity of 100 per cent as a complementary tool in the final diagnosis of acute hepatobiliary pathology. The PPV of SUS was 100 per cent and NPV 81·8 per cent when assessing the accuracy of complementary SUS in detecting the correct diagnosis.

In both groups the patients had to have fasted for 6 h. The mean time to scan was 3·1 h for SUS and 12·0 h for RUS ($P < 0·05$). When considering specific diagnoses, patients with less severe pathology had the longest delay to RUS. The greatest delays for RUS were in patients who either did not have pathology at scan or who were found to have biliary colic (2·5 *versus* 18·7 h for SUS *versus* RUS).

Discussion

Transcutaneous abdominal ultrasonography has not been widely used directly by surgeons in the UK and Ireland. Rather surgeons have relied on radiologists to perform scans on surgical patients. One reason for this has been that ultrasound machines have not been readily available to surgeons and training of surgeons in ultrasonography has not been available. This study supports the hypothesis that ultrasonography can be learnt easily by surgeons and implemented with good result. As yet there are no guidelines for training in ultrasonography for surgeons, although these findings support the concept that adequate training can be achieved following a combination of short didactic and hands-on training courses[3–5].

Ultrasonography is an excellent modality in the assessment of biliary obstruction. In this study all patients with biliary obstruction were diagnosed correctly, although in two of six patients with choledocholithiasis, the stones were not seen in the common duct. These results are similar to those of other studies, in which 30 per cent of common duct stones may not have been visualized at ultrasonography[8,9]. Despite this shortcoming, it is clear that SUS is reliable in detecting biliary obstruction, although determination of the aetiology may require further imaging.

Only four patients (7·5 per cent) had non-hepatobiliary pathology in this cohort. This small percentage reflects the nature of the selection process, which focuses on patients who were believed to have hepatobiliary pathology after clinical assessment.

Patients with isolated biliary colic may not require hospitalization if adequate analgesia can be provided following assessment. The accurate assessment of these patients requires accurate diagnosis of cholelithiasis without signs of acute cholecystitis or biliary dilatation. In this study all patients with biliary colic ($n = 28$) were correctly diagnosed by SUS, and more quickly than with standard RUS. Although the timing of RUS may vary between institutions, a service is not always available outside daytime working hours for biliary colic or otherwise systemically well patients. SUS might therefore facilitate early treatment and discharge. In addition, SUS may reduce outpatient follow-up as a definitive diagnosis of cholelithiasis may be made at initial assessment; therefore interval outpatient scanning and scheduling appointments may not be necessary in patients with uncomplicated biliary colic who have undergone SUS.

In patients with more complex hepatobiliary pathology SUS may provide early diagnostic information, which might be helpful in planning early treatment and intervention; in this setting SUS could be used either alone or as a complementary imaging tool.

SUS for suspected hepatobiliary pathology is an accurate imaging modality that leads to a rapid diagnosis in the emergency setting. With appropriate training, its wider use among surgeons could lead to more efficient systems of care with significant healthcare gains.

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Appraisal of compliance with the UICC/AJCC staging system in the staging of gastric cancer

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Background: In the surgical management of gastric carcinoma, regional lymphatic spread is of prognostic importance. The fifth edition of the Union Internacional Contra la Cancrum classification has been shown to be reproducible, practical and of significant prognostic use. The tumour node metastasis (TNM) system requires at least 15 lymph nodes to be acquired and examined for staging to be accurate. This has raised concern over the consistency with which the requisite numbers of nodes would be acquired. This study was performed to assess how consistently surgically managed cases of gastric cancer in the West Midlands fulfilled this requirement to allow accurate staging.

Methods: Data from the West Midlands Cancer Intelligence Unit on all cases of gastric cancer registered from 1998 to 1999 were obtained and the number of lymph nodes documented for each surgically managed case was assessed.

Results: Overall, only 31.0 per cent of surgically resected cases could be assessed accurately according to the TNM system. The proportion staged accurately varied widely across hospitals from 10·9 to 76·0 per cent.

Conclusion: These results reflect the need for improved N staging across the region to aid the appropriate multimodal treatment of patients.

Paper accepted 11 July 2000

British Journal of Surgery 2002, 89, 1405–1408

Introduction

The prognosis of surgically resected gastric carcinoma is influenced significantly by the presence of lymph node metastases. Definitive staging is performed largely by pathological analysis of the resected specimen. The fifth edition of the Union Internacional Contra la Cancrum (UICC)/American Joint Committee on Cancer (AJCC) tumour node metastasis (TNM) staging system for gastric cancer uses available clinical, radiological, endoscopic or surgical means to assess the extent of malignant disease across three main criteria: the size of the primary lesion and its invasion into tissues, the presence and extent of lymph node metastases, and the presence of distant or non-lymphoid tissue metastasis[1]. The system specifically defines anatomical lymph node sites at which metastatic spread can be said to be regional, and stages disease according to the number of these regional nodes that are found to be involved in the disease process. Extension to non-lymphoid tissue, or lymph nodes outside of these rigidly defined areas, is said to be distant metastasis. To be used accurately the TNM system requires at least 15 lymph nodes to be retrieved and assessed from the resected specimen. This study was performed to assess the proportion of cases of histologically proven gastric carcinoma managed by surgical resection that could be staged satisfactorily in the West Midlands since the new system was published.

Patients and methods

Data were provided from the West Midlands Cancer Intelligence Unit on all cases of gastric cancer registered prospectively in the region for the years 1998–1999, including information on patient demographics, treatment and histopathology. Data were stratified according to

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

hospital and collated according to the number of lymph nodes examined as follows: no nodes sampled, one to four, five to nine, ten to 14, 15–19, 20 or more, and nodes sampled but number not known. The results were then grouped into cases registered with 15 or more nodes sampled, or less than 15 nodes. Registered cases with no nodes sampled were reviewed and their management appraised.

Table 1 Management of cases of histologically verified gastric cancer

Hospital	Total cases proven histologically	Managed non-surgically	Managed surgically
A	112	66 (58·9)	46 (41·1)
B	42	24 (57·1)	18 (42·9)
C	89	46 (51·7)	43 (48·3)
D	117	70 (59·8)	47 (40·2)
E	86	47 (54·7)	39 (45·3)
F	63	45 (71·4)	18 (28·6)
G	29	17 (58·6)	12 (41·4)
H	60	28 (46·7)	32 (53·3)
I	126	66 (52·4)	60 (47·6)
J	49	24 (49·0)	25 (51·0)
K	68	41 (60·3)	27 (39·7)
L	81	49 (60·5)	32 (39·5)
M	49	30 (61·2)	19 (38·8)
N	200	129 (64·5)	71 (35·5)
O	141	85 (60·3)	56 (39·7)
P	53	28 (52·8)	25 (47·2)
Q	77	48 (62·3)	29 (37·7)
R	141	66 (46·8)	75 (53·2)
Other	61	36 (59·0)	25 (41·0)
Total	1644	945 (57·5)	699 (42·5)

Values in parentheses are percentages

Results

For the period 1998–1999, 2056 cases of gastric cancer were registered across 18 hospitals, and a further group of institutions including private hospitals, community/mental institutions and unknown sources. Of these cases, 1644 (80·0 per cent) were histologically proven. Of the histologically proven cancers, 699 (42·5 per cent) were managed surgically and the other 945 (57·5 per cent) were treated by palliative or medical means. *Table 1* shows the number of cases of histologically proven gastric cancer managed surgically according to hospital. *Table 2* shows the proportion of these surgical cases that contained at least 15 lymph nodes, and so were amenable to accurate staging. Overall for the region, 31·0 per cent of surgically resected cases could be staged accurately; performance across hospitals varied from 10·9 to 76·0 per cent of cases. The performance across the region is shown in *Fig. 1*.

Table 3 shows the proportion of accurately staged gastric cancers registered by hospital in relation to workload (number of patients) and numbers of operations performed.

Discussion

Definitive staging of gastric cancer relies heavily on accurate pathological analysis. It has been shown that

Table 2 Percentage of cases of surgically managed gastric cancer amenable to accurate staging by hospital

Hospital	Cases managed surgically	Inadequate nodes or nodes not known	15 or more nodes	Percentage of surgical cases staged accurately
A	46	41	5	10·9
B	18	16	2	11·1
C	43	37	6	14·0
D	47	40	7	14·9
E	39	33	6	15·4
F	18	15	3	16·7
G	12	10	2	16·7
H	32	25	7	21·9
I	60	46	14	23·3
J	25	19	6	24·0
K	27	19	8	29·6
L	32	22	10	31·3
M	19	13	6	31·6
N	71	48	23	32·4
O	56	36	20	35·7
P	25	14	11	44·0
Q	29	16	13	44·8
R	75	18	57	76·0
Other	25	14	11	44·0
Total	699	482	217	31·0

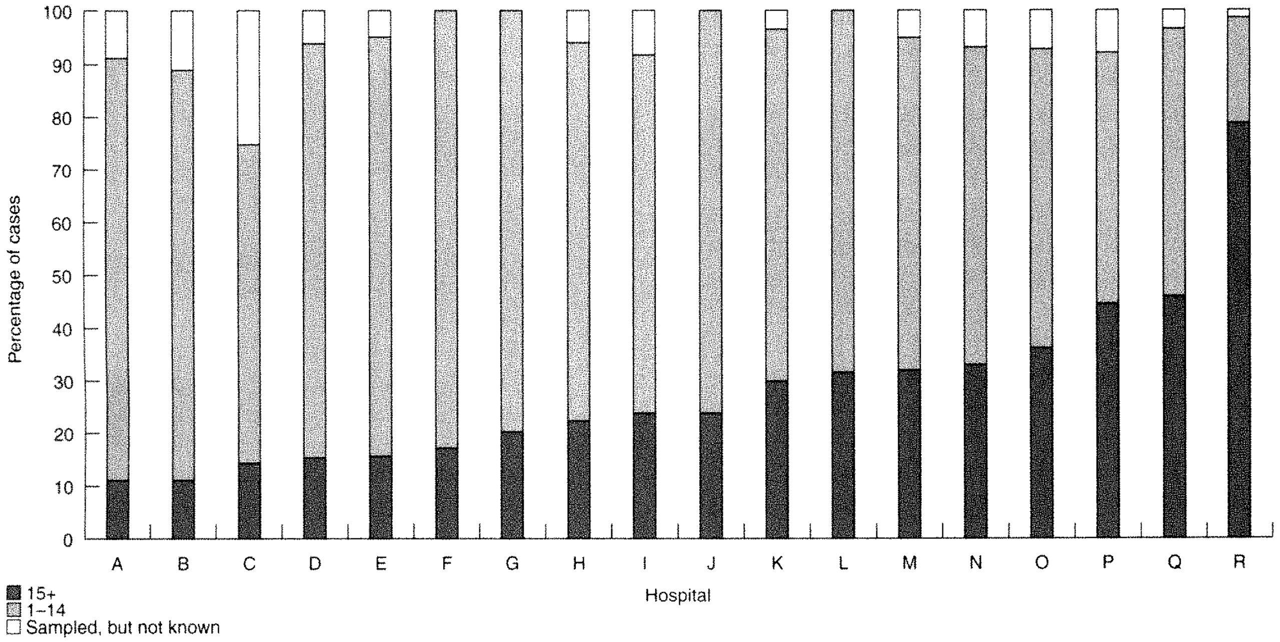

Fig. 1 Percentage of histologically verified cases by number of nodes sampled

Table 3 Workload according to hospital in relation to accurate staging

Hospital	Total cases registered	Surgical resections	Percentage staged accurately
A	127	46	10·9
B	49	18	11·1
C	101	43	14·0
D	127	47	14·9
E	96	39	15·4
F	69	18	16·7
G	33	12	16·7
H	73	32	21·9
I	140	60	23·3
J	56	25	24·0
K	75	27	29·6
L	93	32	31·3
M	55	19	31·6
N	244	71	32·4
O	160	56	35·7
P	72	25	44·0
Q	90	29	44·8
R	162	75	76·0
Other	234	25	44·0
Total	2056	699	31·0

preoperative N staging of disease using widely available imaging modalities (i.e. computed tomography and magnetic resonance imaging) is of limited reliability[2]. Methods of pathological staging have been problematic and varied. Early staging systems essentially differentiated only between lymph node-positive and -negative disease[3]. The Japanese classification[4], which uses information on the anatomical position of lymph node metastases, represented a significant development in the differential prognosis of node-positive disease and has been considered the gold standard for decades. The system is relatively poorly reproducible, however, as it relies on meticulous dissection by the surgeon of the fresh specimen. The current edition of the UICC/AJCC TNM system, available since 1997, derives prognostic information from the number of involved lymph nodes[5]. This has been shown to relate to prognosis[6]. Studies have compared it to the previous fourth edition[7,8] and the Japanese classification[9–11], and results have demonstrated that it has greater prognostic power than these other systems. It is more reproducible than the Japanese system in that the pathologist is largely responsible for dissection of the requisite number of lymph nodes from the specimen[12]. Concerns have been raised, however, over the proportion of cases of surgically resected stomach cancer that will contain enough lymph nodes to satisfy the requirements of this TNM system. It has been demonstrated that the system is less accurate if less than the minimum number of 15 lymph nodes is available[7,13]. This can affect prognosis as the ratio of lymph nodes found to have metastatic disease as a proportion of total lymph nodes dissected is a significant predictor of outcome[14].

This study was performed to ascertain whether hospitals in the West Midlands region were staging gastric cancer appropriately. The figures presented show that the TNM staging system is not being entirely fulfilled in a significant proportion of cases. First, not all cases of gastric cancer have a tissue diagnosis. This is an absolute requisite[5]. In the region overall, 80·0 per cent of registered cases had a tissue diagnosis. This is an improvement on previously published figures for the region which indicated that 46·3 per cent of cases had a tissue diagnosis[15]. Second, not all cases of histologically confirmed gastric cancer that are surgically managed have the minimum requisite number of nodes for accurate TNM staging. Other series have published rates of between 13 and 37 per cent of surgically resected cases with less than 15 lymph nodes isolated. The present results across the region do not compare favourably although these other series involved only tertiary centres where gastric surgery was the recognized area of expertise[7,10]. This has implications for both prognosis as assessed by the TNM system, and possibly absolute prognosis in relation to stage migration and the shifting of patients into more favourable prognostic groups where appropriate[16].

The effort required by the pathologist to retrieve and section the required number of lymph nodes is considerable. In smaller units, there may not be the resources available to do this in every case. Feedback from clinicians may also be limited. The figures for departmental workload (*Table 3*) demonstrate that busier centres in the region are not managing the pathology better than units in which gastric cancer is seen relatively rarely. The importance of accurate staging is emphasized, particularly in multidisciplinary meetings in which close communication between surgeons, pathologists and oncological specialists ensures that multimodal treatment is considered and implemented where appropriate, or where valid clinical research would have perceived benefits in the future[17]. The emergence of regional cancer networks also demands accurate staging of disease for registries, and facilitates the construction of a database for statistical purposes and clinical audit. The figures above, derived from the West Midlands Cancer Intelligence Unit, demonstrate the power of these networks to audit clinical effectiveness and drive changes in practice where needed. Assessment of the staging of gastric cancer in the future will hopefully demonstrate further improvements in practice as regional protocols become more established.

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p53, DCC and thymidylate synthase as predictors of survival after resection of hepatic metastases from colorectal cancer

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Background: Hepatic metastasis from colorectal cancer is a common problem. Hepatic resection offers the only chance of cure. Prognosis of patients following hepatic resection is currently based on clinicopathological factors (of both the primary cancer and the hepatic metastasis), which do not accurately predict the subsequent behaviour of the tumour. The aim of this study was to evaluate three molecular genetic markers – p53, DCC (deleted in colonic cancer) and thymidylate synthase – in both the primary colorectal tumour and the resected hepatic metastases, and to determine their correlation, if any, with survival in patients with resected hepatic metastases from colorectal cancer.

Methods: Sixty-three patients with hepatic metastases and 40 corresponding colorectal primary tumours were studied using immunohistochemical staining for p53, DCC and thymidylate synthase, as well as *p53* gene mutations using polymerase chain reaction–single-stranded conformational polymorphism (PCR-SSCP) analysis. The results were correlated with survival.

Results: There was no correlation between p53, DCC or thymidylate synthase immunohistochemical staining, or between *p53* PCR-SSCP analysis, and survival for either hepatic metastases or the colorectal primary tumour.

Conclusion: Prediction of prognosis in patients having resection of hepatic metastases from colorectal cancer continues to be problematic. Other genetic markers or combination of markers need to be evaluated.

Paper accepted 13 June 2002

British Journal of Surgery 2002, **89**, 1409–1415

Introduction

Colorectal cancer is a major cause of morbidity and mortality, and is the second most common cancer in both men and women worldwide. In the USA it accounts for approximately 150 000 new cases and 60 000 deaths each year[1]. The most frequent site of metastasis from colorectal cancer is the liver. Up to 35 per cent of patients with colorectal cancer will have hepatic metastases at the time of operation for the primary lesion, and a further 8–25 per cent will develop metachronous hepatic metastases after primary resection[2,3].

Patients with untreated liver metastases have a median survival of less than 12 months and a 5-year survival rate of almost zero[4,5]. Hepatic resection offers the only chance of cure for metastases confined to the liver. A 5-year survival rate of 25–35 per cent has been reported for patients with apparently resectable metastases[6–9].

Various prognostic factors have been shown to influence the outcome of patients following resection of colorectal liver metastases[10]. The literature regarding prognostic indicators is confusing, partly because of the relatively small numbers of patients included in studies. However, many authors agree that the presence of more than three metastatic deposits, involved resection margins, extrahepatic disease or nodal spread at the primary tumour site is likely to be associated with worse survival following hepatic resection[10]. Analysis of these factors may assist in selecting patients most likely to benefit from resection, but they do not accurately predict the subsequent behaviour of the tumour[11].

Genetic changes accumulate in the progression from colorectal adenoma to carcinoma[12]. Mutations involving specific genes may provide a better guide to tumour behaviour than clinical and pathological features, and thereby assist in predicting patient outcome. The aim of this study was to evaluate the status of three genetic markers, p53, deleted in colonic cancer (DCC) and thymidylate synthase, and to determine any association with survival in patients with resected hepatic metastases from colorectal cancer. The markers were assessed in both the primary colorectal tumour and the resected hepatic metastases.

Patients and methods

Clinical

Between January 1988 and December 1997, 72 patients with isolated hepatic metastases from colorectal cancer underwent resection at Sydney's Royal Prince Alfred Hospital. All patients had four or fewer hepatic metastases and no apparent extrahepatic disease after preoperative assessment with computed tomography (CT) (with or without ultrasonography of the abdomen) and hepatic angiography. In addition, positron emission tomography (PET) was performed after 1993. Assessment also included chest radiography and liver function tests. CT of the thorax was undertaken only if an abnormality was found on chest radiography or PET.

Laboratory methods

Tissues

Archival formalin-fixed, paraffin wax-embedded tissues from both the primary cancer and the resected hepatic metastases were retrieved.

A single block of the tumour was used for immunohistochemistry (IHC) and for polymerase chain reaction–single-stranded conformational polymorphism (PCR-SSCP) analysis. Several 10-μm sections were cut for DNA extraction and four 5-μm sections were used for IHC staining.

p53, DCC and the enzyme thymidylate synthase were assessed by means of IHC. In addition, *p53* gene mutations were evaluated by PCR-SSCP analysis.

Immunohistochemistry

Slide-mounted sections were stained using routine IHC antigen retrieval methods (Trizma-buffered saline with ethylenediamine tetra-acetic acid (EDTA) solution and microwave) and the avidin–biotin complex methodology (based on Dako Universal LSAB+ kit streptavidin®; Dako, Carpinteria, California, USA)[13]. The primary antibodies used were monoclonal mouse antihuman Dako p53 protein DO-7® (Dako) at 1 : 800 dilution, DCC antibody PharMingen G97/499® (PharMingen, San Diego, California, USA) at 1 : 400 dilution, and thymidylate synthase antibody at 1 : 1000 dilution. The chromogen solution contained diaminobenzoate. Preparations in which the primary antibody was omitted were used as negative controls, and established positive staining slides were used as positive controls in each run.

p53 positivity was determined by the presence of brown reaction product within the nuclei of neoplastic cells. Tumours were classified as negative (no nuclear staining) or positive (any number of nuclei staining). If positive, an assessment of the percentage of tumour cells staining was made according to the method described by Fu *et al.*[14]. In summary, a score of 1–5 was assigned according to the percentage of positively stained tumour cells: 1, less than 5 per cent positively stained; 2, 5–25 per cent stained; 3, 26–50 per cent stained; 4, 51–75 per cent stained; 5, more than 75 per cent stained. A further score was assigned according to the intensity of staining: 1, weak; 2, moderate; 3, intense. The percentage and intensity scores were subsequently multiplied to produce a weighted score for each specimen. A score of 6 or more was arbitrarily chosen to represent positive staining. DCC- and thymidylate synthase-positive reactions required the presence of brown reaction product in the cytoplasm of neoplastic cells. DCC and thymidylate synthase IHC findings were also assessed semiquantitatively using a similar technique. Scoring was performed independently by two observers. In cases of disagreement, the final score was determined by consensus.

DNA extraction and polymerase chain reaction

Using the method of Levi *et al.*[15], 10-μm sections were prepared as substrate for DNA amplification. Exons 5–8 of the *p53* gene were amplified separately using primers and methodology provided by Dix *et al.*[16].

Polymerase chain reaction–single-stranded conformational polymorphism

A 2-μl volume of PCR product was diluted in 20 μl formamide loading buffer (95 per cent formamide, EDTA 20 mmol/l, pH 8·0, 0·05 per cent bromophenol blue and 0·05 per cent xyanol cyanol) and denatured by boiling for 10 min. Denatured samples were loaded on a 10 per cent polyacrylamide gel (100 × 105 mm) and run at 20 mA for 4 h. The gels were then silver-stained using the technique described by Budowle *et al.*[17]. The first 20 samples displaying mutant bands were reamplified and SSCP analysis was repeated to confirm an aberrant band.

Statistical analysis

Survival was calculated from the time of hepatic resection. Recurrences were detected by clinical examination, radiography and/or biopsy performed at 6-month intervals for 2 years, and then yearly. The χ^2 test and Fisher's exact test (when the number of patients was less than five) were used for statistical analysis.

Results

Patient demographics

Sixty-three of the 72 patients who had a liver resection for metastases from colorectal cancer were included in the study. Nine patients were excluded because of loss to follow-up or because tissue for laboratory assessment was not available. Thirty-one patients were men and 32 were women, with a median age of 59 (range 32–80) years. Thirty-four right hemihepatectomies, seven extended right hemihepatectomies and 22 left hemihepatectomies were performed. Fifteen patients had separate wedge excisions in addition to formal hepatectomy.

At operation nine patients were found to have extra-hepatic disease. Of these, seven had local extension of tumour, most commonly to the right hemidiaphragm.

On histopathological review of the hepatic metastases, 44 patients (70 per cent) had only a single metastasis, eight (13 per cent) had two or three metastases, and 11 (17 per cent) had four or more metastases despite preoperative assessment. Eight patients (13 per cent) had involved resection margins, and of the remainder 20 patients (32 per cent) had resection margins of less than 10 mm.

Of the 48 patients who developed disease recurrence, tumour recurred solely in the liver in 16 patients (33 per cent). Twenty-two (35 per cent) of the 63 patients were alive or died without disease at a mean follow-up of 73 (range 23–141) months. Median survival was 24·5 (range 0–89) months. The 1-, 2- and 5-year cancer-specific survival rates were 92, 65 and 22 per cent respectively.

Laboratory results

There was close agreement for scoring of IHC staining between observers. Forty-four per cent (28 of 63) of hepatic tumours were IHC p53 positive (indicating mutant p53 protein), 70 per cent (44 of 63) were DCC negative (indicating lack of DCC protein) and 46 per cent (29 of 63) were thymidylate synthase positive. No significant correlation was found between the IHC status of each of the three markers and cancer-specific survival (*Table 1*). *Figs 1* and *2* show examples of p53 and DCC IHC-positive staining.

Fifty-eight per cent (35 of 60) of hepatic tumours were found to have abnormal *p53* PCR-SSCP band protein for at least one exon. There was no correlation between *p53* PCR-SSCP and overall cancer-specific survival (*Table 2*). It was not possible to extract DNA from one specimen or to amplify an exon in four samples (in two of these samples abnormalities were present in other exons and these were

Table 1 Correlation of immunohistochemistry of hepatic metastases with cancer-specific survival

IHC	Cancer-specific survival	*P**
p53		0·07
Negative	9 of 35	
Positive	13 of 28	
DCC		0·53
Negative	15 of 44	
Positive	7 of 19	
Thymidylate synthase		0·42
Negative	11 of 34	
Positive	11 of 29	

IHC, immunohistochemistry; DCC, deleted in colonic cancer. *χ^2 test

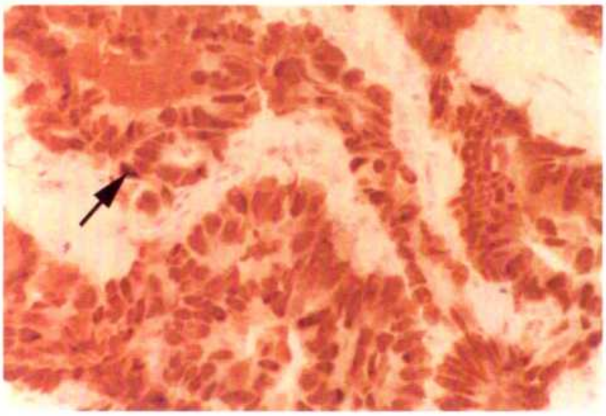

Fig. 1 p53-positive immunohistochemistry of colorectal adenocarcinoma (magnification × 40). Carcinoma nuclei are stained intensely brown (arrow), with very slight staining of the cytoplasm

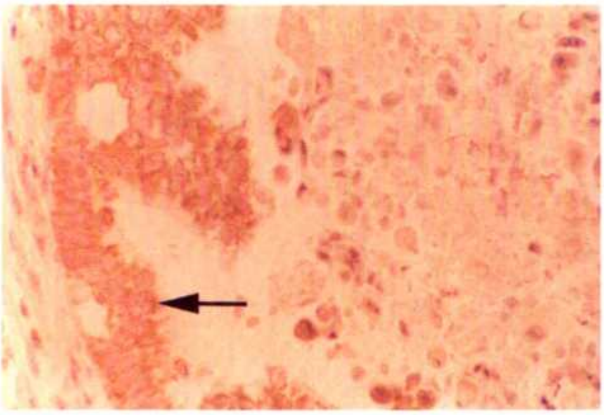

Fig. 2 Deleted in colonic cancer (DCC)-positive immunohistochemistry of colorectal adenocarcinoma (magnification × 40). The cytoplasm is stained brown (arrow); the nuclei are stained the normal pink. Thymidylate synthase-positive staining is similar

included in the overall analysis as having abnormal *p53* PCR-SSCP).

Forty primary cancers were located, 15 of which were p53 IHC positive, 28 were DCC negative and 29 were thymidylate synthase positive.

It was not possible to extract DNA from one tumour or to amplify an exon in two samples. Of the 37 primary tumours available for analysis, 15 were found to have abnormal *p53* PCR-SSCP. When IHC staining and *p53* PCR-SSCP findings of the colorectal primary were assessed with regard to cancer-specific survival following hepatic resection for metastases, again no significant correlation was found (*Tables 3* and *4*).

Table 2 Correlation between *p53* polymerase chain reaction–single-stranded conformational polymorphism of hepatic metastases and overall cancer-specific survival

p53 PCR-SSCP	Cancer-specific survival	*P**
Exon 5		0·38
Normal	15 of 48	
Abnormal	6 of 12	
Exon 6		0·36
Normal	17 of 47	
Abnormal	4 of 15	
Exon 7		0·22
Normal	18 of 48	
Abnormal	3 of 14	
Exon 8		0·58
Normal	18 of 52	
Abnormal	3 of 8	
Any mutation		0·89
None	9 of 25	
Present	12 of 35	

PCR-SSCP, polymerase chain reaction–single-stranded conformational polymorphism. *χ^2 or Fisher's exact test

Table 3 Correlation of immunohistochemistry of colorectal primary tumour and overall cancer-specific survival

IHC	Cancer-specific survival	*P**
p53		0·34
Negative	7 of 23	
Positive	6 of 14	
DCC		0·60
Negative	9 of 26	
Positive	4 of 11	
Thymidylate synthase		0·31
Negative	5 of 11	
Positive	8 of 26	

IHC, immunohistochemistry. *χ^2 or Fisher's exact test

Table 4 Correlation between *p53* polymerase chain reaction–single-stranded conformational polymorphism of the colorectal primary tumour and overall cancer-specific survival

p53 PCR-SSCP	Cancer-specific survival	*P**
Exon 5		0·54
Normal	9 of 28	
Abnormal	3 of 8	
Exon 6		0·44
Normal	10 of 30	
Abnormal	2 of 4	
Exon 7		0·66
Normal	12 of 34	
Abnormal	0 of 1	
Exon 8		0·58
Normal	11 of 32	
Abnormal	1 of 3	
Any mutation		0·88
None	6 of 19	
Present	6 of 15	

PCR-SSCP, polymerase chain reaction–single-stranded conformational polymorphism. *χ^2 or Fisher's exact test

Table 5 Change in status between primary tumour and hepatic metastasis

	p53	DCC	Thymidylate synthase	*p53* PCR-SSCP
Primary tumour negative, hepatic metastasis positive	4	6	2	11
Primary tumour positive, hepatic metastasis negative	0	7	18	4
Primary tumour and hepatic metastasis similar	36	27	20	22

DCC, deleted in colonic cancer; PCR-SSCP, polymerase chain reaction–single-stranded conformational polymorphism

Several tumours showed altered staining status when the primary tumour was compared with the hepatic metastasis. This is shown in *Table 5*.

Discussion

The conventional approach to determine prognosis in patients with hepatic metastases from colorectal cancer is based on clinicopathological variables, such as stage and grade of the primary tumour, presence of extrahepatic disease, number of metastases present in the liver and resection margin status. This also determines the therapeutic approach. Recent advances in the understanding of tumour biology and molecular genetics may assist in the assessment of prognosis and therefore affect treatment strategies.

There are only limited data available on biological prognostic factors in liver metastases from colorectal cancer. The majority of studies have concentrated on DNA ploidy or *p53* mutations. Studies of DNA ploidy in hepatic metastases have suggested that patients with aneuploid tumour cell populations (rather than the normal diploid) have a shorter survival and that DNA ploidy is a significant prognostic indicator for resected hepatic metastases[18,19].

The *p53* gene encodes a nuclear phosphoprotein that regulates cell proliferation. Lack of functional p53 as a result of deletion or mutation allows uncontrolled progression through the cell cycle[20]. The p53 status of a colorectal cancer appears to predict prognosis, with *p53* mutation or altered expression correlating with a poorer survival[21,22]. The picture is not so clear regarding resected hepatic metastases. Some authors have suggested that p53 IHC staining is a significant prognostic indicator after hepatic resection[23–25]. Pocard *et al.*[26] reported a trend towards a poorer prognosis, although this was not statistically significant. Costa *et al.*[18] and the present study, however, have found no correlation between p53 IHC status and survival after resection of hepatic metastases.

There are a few possible reasons for the discrepancy in results. First, all of these studies, including the present one, included only relatively small numbers of patients. Second, technical conditions may influence the quality of IHC staining. The above studies used different antibodies for p53 and slightly different detection systems. According to Baas *et al.*[27], the selection of the primary antibody and application of an antigen retrieval system to detect the antibody are of great importance in optimizing IHC staining. These authors recommend the use of DO-7 antibody, as used in the present study. In addition, the number and intensity of p53-positive cells often varies in different tumours, with studies using an arbitrary cut-off for negativity and positivity[28,29]. Even within the same tumour, the number and intensity of p53-positive cells may vary, making it difficult to quantify the p53 status of a tumour[27]. The scoring method of Fu *et al.*[14] used in this study appears to be the most satisfactory at this point in time. There was close agreement in scoring between the observers in the present study, as found in the authors' previous study[30].

Loss of heterozygosity (LOH) for *p53* in the primary cancer has been shown to correlate with the presence of metastases[31], and a high frequency of *p53* LOH has been reported in hepatic metastases from colorectal cancer[32]. To date, no study has correlated LOH of *p53* with prognosis in resected hepatic metastases from colorectal cancer.

There is only one study that has assessed *p53* status using PCR-SSCP analysis and related this to prognosis in resected hepatic metastases from colorectal cancer[33]. The authors studied samples from both the primary tumour and the hepatic metastases of 36 patients and, as in the present study, found that *p53* PCR-SSCP did not correlate with survival.

DCC is a candidate tumour suppressor gene on chromosome 18q[34]. There is reduced or absent expression of DCC in many colorectal cancers. Absence of DCC IHC staining has been associated with a poor prognosis in colorectal cancer[35,36], and has also been shown to predict the appearance of hepatic metastases[37]. Ookawa *et al.*[38] noted that hepatic metastases manifest a higher proportion of tumour cells with lack of DCC staining compared with the primary cancer, similar to the findings in this study. No other report has assessed DCC IHC staining in relation to outcome after resection of hepatic metastases.

Thymidylate synthase is an enzyme that is integral to DNA synthesis. In the present study, a higher thymidylate synthase positivity rate was found in the primary tumour compared with that in metastases. The significance of this is not known, but it may indicate a higher propensity for abnormal growth in the metastatic lesion.

Prognosis in patients undergoing resection of hepatic metastases from colorectal cancer is difficult to predict. This study suggests that evaluation of p53, DCC and thymidylate synthase from either the primary tumour or the metastases does not predict prognosis. Several issues need to be addressed in further studies. First, an optimized method of IHC staining needs to be established between different laboratories. This would include using the most sensitive antibody for staining. A standardized method of assessing the degree of positivity or negativity of staining would also be helpful to compare the results between different institutions. Second, studying a larger cohort of patients may assist in improving the strength of further studies. Third, other molecular markers or combination of markers need to be assessed.

Acknowledgements

R.P.M.S. was supported by the Sir Roy McCaughey Surgical Research Scholarship from the Royal Australasian College of Surgeons.

The authors thank Dr G. W. Aherne, Institute of Cancer Research, Sutton, UK, for supplying the thymidylate synthase antibody; Y. Kwun, Scientific Officer, Department of Anatomical Pathology, Concord Hospital, Sydney; the staff of the Department of Anatomical Pathology, Royal Prince Alfred Hospital, Sydney; and Professor P. Chapuis, Department of Surgery, Concord Hospital and the University of Sydney, Australia.

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Original article

Ranitidine as adjuvant treatment in colorectal cancer

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Background: Results from short-term studies of histamine type 2 (H_2) receptor antagonists on survival of patients with solid tumours are debatable. In this study the efficacy of the H_2-receptor antagonist ranitidine on long-term survival of patients with colorectal cancer was evaluated.

Methods: Patients scheduled for elective resection of primary tumours were consecutively included in a randomized double-blind placebo-controlled clinical study designed to evaluate the effect of ranitidine on survival. Before skin incision ranitidine 100 mg or placebo was given intravenously twice daily followed by oral ranitidine 150 mg or placebo twice daily for 5 years. Adjuvant cytotoxic or radiation therapy was not given. An observer-blinded interim analysis performed after 40 months showed that there was no effect of ranitidine on overall survival, and the study was discontinued in accordance with the protocol. The patient cohort has been followed continuously without loss of any patient, and a final statistical analysis was performed on an intention-to-treat basis after more than 5 years; this included a subgroup analysis of perioperative blood transfusion and postoperative infectious complications.

Results: The median observation period of the 740 patients included was 6·8 (range 5·4–7·9) years. A univariate analysis of all 740 patients and of the subgroup of 560 who underwent curative resection showed no significant effect of ranitidine on survival. Furthermore, ranitidine had no survival benefit in curatively resected patients who received a perioperative blood transfusion ($n = 358$), but it improved the survival of non-transfused patients ($n = 202$; hazard ratio (HR) 0·6 (95 per cent confidence interval (c.i.) 0·4 to 0·9), $P = 0·02$) and of non-transfused patients who did not develop postoperative infectious complications ($n = 170$; HR 0·6 (95 per cent c.i. 0·4 to 0·9), $P = 0·01$). In multivariate analysis of patients who had a curative resection, including Dukes' stage, age, gender, tumour location, blood transfusion, postoperative infectious complications and treatment, ranitidine still had an independent, beneficial effect on survival (HR 0·6 (95 per cent c.i. 0·4 to 1·0), $P = 0·04$) within the subgroup of patients who did not receive perioperative blood transfusion and did not develop postoperative infectious complications.

Conclusion: Ranitidine may prolong the survival of patients who undergo curative resection of colorectal cancer and who do not receive perioperative blood transfusion and do not develop postoperative infectious complications.

Presented to the annual meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, March 2001, and published in abstract form as *Proceedings of the American Association for Cancer Research* 2001; **42:** 3747

Paper accepted 20 June 2002

British Journal of Surgery 2002, **89**, 1416–1422

Introduction

Histamine has been shown to participate in regulation of the immune response[1], acting via specific histamine type 1 (H_1) and type 2 (H_2) receptors. It may act as an immunostimulant in physiological concentrations primarily via binding to H_1 receptors[2] and to a certain extent via binding to H_2 receptors[2,3]. At increased, pathophysiological, concentrations histamine may bind preferentially to H_2 receptors and thereby reduce overall immune competence[1,2,4–6]. Consequently, histamine has been suggested to play a stimulatory role in the regulation of tumour growth acting via H_2 receptors[7,8], and H_2-receptor antagonists have been shown to attenuate experimental tumour growth[7,8]. The mechanisms leading to beneficial effects of H_2-receptor antagonists have not been clarified fully, but were originally supposed to be related to improvement in the overall impairment of immune competence in patients with malignant disease[1,9].

Some clinical studies have shown positive effects of H_2-receptor antagonists in patients with colorectal[10,11] and gastric[12] cancer, but other studies have not been supportive[13–15]. From April 1991 to August 1993, 823 patients over 18 years of age were included in a Danish–Scottish multicentre double-blind placebo-controlled clinical study of the efficacy of the H_2-receptor antagonist ranitidine on patients undergoing elective surgery for large-bowel tumours. A scheduled observer-blinded interim analysis of the overall effect of ranitidine *versus* placebo, performed after a median observation period of 40 months, showed that ranitidine had no effect on overall survival of patients who underwent elective resection of colorectal cancer[16]. Therefore, the study was discontinued in early 1996.

According to the protocol a final statistical analysis of the effect of ranitidine would be performed after observation of all patients for more than 5 years. The final evaluation should include subgroup analysis based on various prognostic variables, which, except for perioperative blood transfusion and postoperative infectious complications, were not specified in the protocol. The aim of the present study was therefore to perform a final subgroup analysis, particularly in the light of recent findings of the effect of H_2-receptor antagonists on angiogenesis[17–19] and the role of perioperative blood transfusion and postoperative infectious complications on cancer recurrence and survival[20–23].

Patients and methods

Details of inclusion criteria, medication, surgical procedures, perioperative blood component transfusion, postoperative infectious complications, pathology and histology, laboratory analyses, and recording of data have been listed in previous papers[16,24]. In brief, at inclusion all patients were without clinical signs and symptoms of infectious disease, and none had been treated with systemic steroids, antibiotics, antiviral drugs, H_2-receptor antagonists or cytotoxic agents within 2 weeks before study entry. Patients with severe concurrent illness, such as leukaemia or human immunodeficiency virus (HIV) infection, and those undergoing chemotherapy, radiotherapy and/or any other therapy for cancer or expected to undergo such therapies within the study period were not included. Furthermore, patients with reduced renal function and those unable to comply with the requirements of the protocol were not allowed to participate in the study. The patients received ranitidine 100 mg or placebo intravenously twice daily from just before skin incision, followed by oral ranitidine 150 mg or placebo twice daily for 5 years or until death or withdrawal.

All surgical procedures were recorded. The study was performed before total mesorectal excision had been introduced in Denmark. The amount and exact component of blood transfused from 1 month before to 1 month after operation, as well as all postoperative infectious complications, were recorded.

Originally, the study comprised patients from Denmark and Scotland. After discontinuation of the study the Scottish patients ($n = 83$) were lost to follow-up. All the Danish patients ($n = 740$) were followed until death by means of the computerized Central Personal Registration. The present analysis includes all the Danish patients with colorectal adenocarcinoma on an intention-to-treat basis. Patients who decided to withdraw from the study were not referred to chemotherapy or radiotherapy, as these procedures were not part of the standard treatment regimen recommended for patients with colorectal cancer in Denmark at that time.

The patients were assessed during hospitalization, 1 month after operation and every 3 months thereafter until withdrawal, death or discontinuation of the study. The disease was staged according to Dukes' original classification with addition of a 'D' group, which identified patients with distant metastasis. Data on cancer-specific death were not available, primarily owing to the reduced number of autopsies performed in Denmark. The survival analysis was based on overall survival (death from all causes); the expected mortality rate from all causes was calculated in a cohort with the same age and gender distribution as the studied patients[25] using the vital statistics of the Danish population[26].

The Central Ethics Committee, Danish Board of Health and Danish Data Protection Agency approved the study.

An SAS® software package (version 6.12; SAS Institute, Cary, North Carolina, USA) was used to manage patient data and to perform statistical analyses. The Kaplan–Meier method was used to estimate survival probabilities, and the log rank test to test for equality of strata. The Cox proportional hazards model was used for multivariate analysis. The assumption of proportional hazards was verified graphically where applicable. $P < 0.05$ was considered significant.

Results

The median observation period was 6·8 (range 5·4–7·9) years and none of the 740 patients was lost to follow-up. The median age was 69 (range 30–90) years; there were 294 women and 446 men. Within the observation period 494 patients died (67 per cent). All patients had histologic-

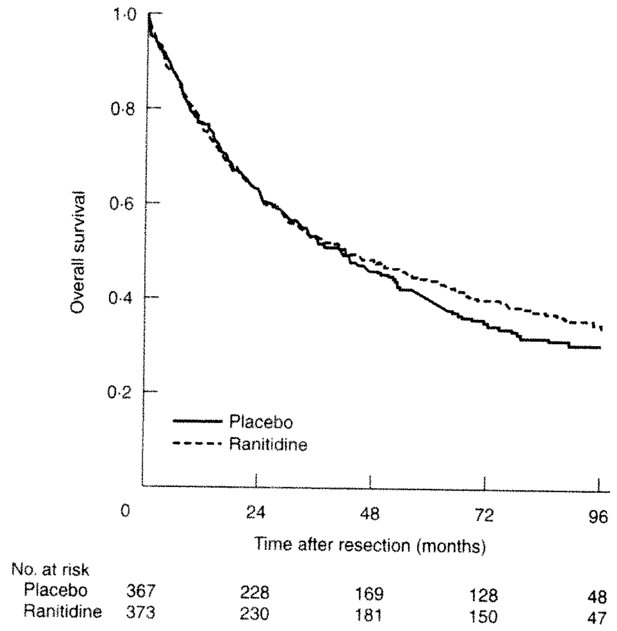

Fig. 1 Overall survival of 740 patients who had resection of primary colorectal cancer and were randomized to receive ranitidine or placebo

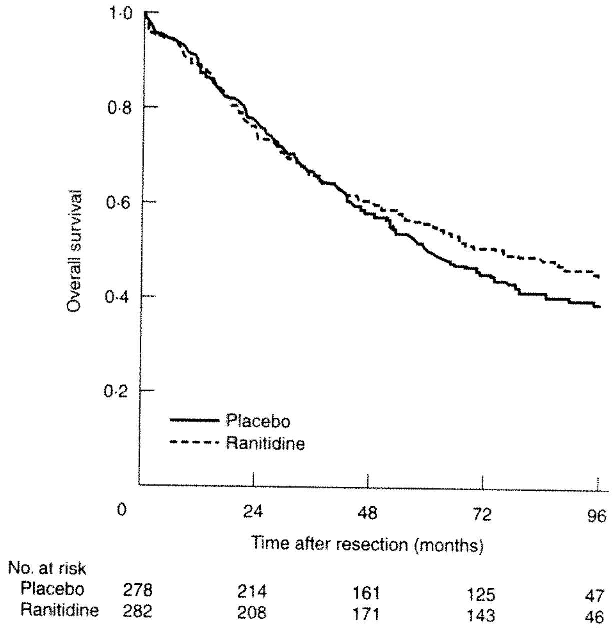

Fig. 2 Overall survival of 560 patients who had curative resection of primary colorectal cancer and were randomized to receive ranitidine or placebo

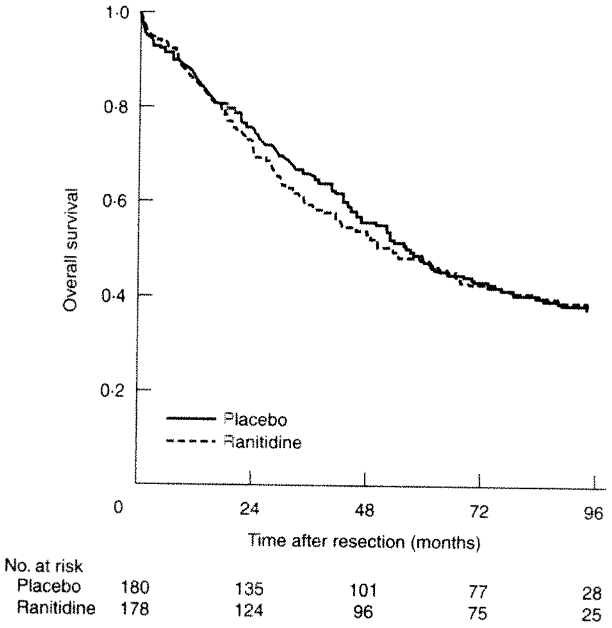

Fig. 3 Overall survival of 358 patients who had curative resection of primary colorectal cancer and were randomized to receive ranitidine or placebo, and who received perioperative blood transfusion

ally verified adenocarcinoma of the colon (419 patients) or rectum (321 patients). The Dukes' stage of disease was: A, 63 patients; B, 275 patients; C, 212 patients; and 'D', 190 patients. Five hundred and sixty of the 740 patients underwent macroscopically curative resection including ten with Dukes' 'D' disease, who had a solitary tumour in the liver removed during the operation.

Blood components, such as non-leucocyte-filtered, buffy coat-depleted blood, fresh frozen plasma and/or platelet preparations, were transfused into 64 per cent of the patients who had a curative operation. Development of postoperative infectious complications, such as wound infection, septicaemia, pneumonia, anastomotic leakage, intra-abdominal abscess and/or perineal wound infection, was verified in 27 per cent of the patients. Urinary tract infections were included only when complicated with septicaemia. Thirty-four patients (6 per cent) underwent reoperation for anastomotic leakage within the first month.

A univariate analysis of all 740 patients (*Fig. 1*) and of the patients who had curative resection (*Fig. 2*) showed that there was no effect ($P < 0{\cdot}3$ and $P < 0{\cdot}2$ respectively) of ranitidine on survival. Furthermore, ranitidine had no effect on survival of the 358 patients who underwent curative resection and received a perioperative blood transfusion ($P = 0{\cdot}79$) (*Fig. 3*). However, ranitidine prolonged survival among non-transfused patients ($n = 202$) (hazard ratio (HR) 0·6 (95 per cent confidence interval (c.i.) 0·4 to 0·9), $P = 0{\cdot}02$) (*Fig. 4*). In the subgroup of patients who did not receive perioperative blood transfusion and did not develop infectious complications ($n = 170$) ranitidine prolonged survival (HR 0·6 (95 per cent c.i. 0·4 to 0·9), $P = 0{\cdot}01$)

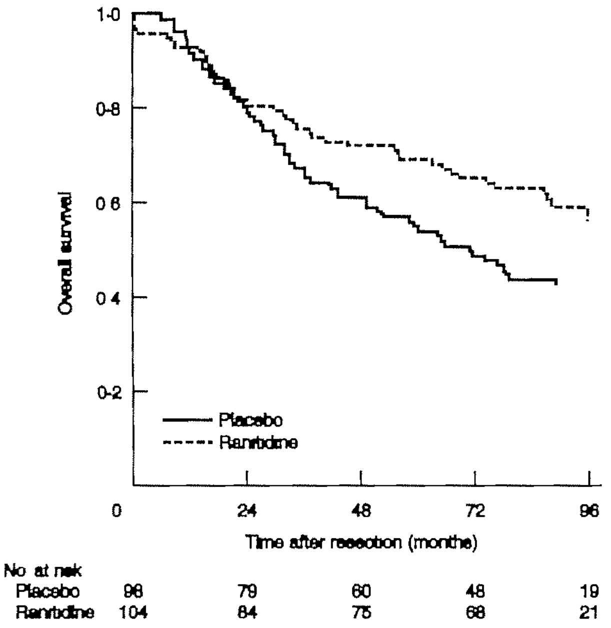

Fig. 4 Overall survival of 202 patients who had curative resection of primary colorectal cancer and were randomized to receive ranitidine or placebo, and who did not receive perioperative blood transfusion. Hazard ratio 0·6 (95 per cent confidence interval 0·4 to 0·9); $P = 0·02$ (log rank test)

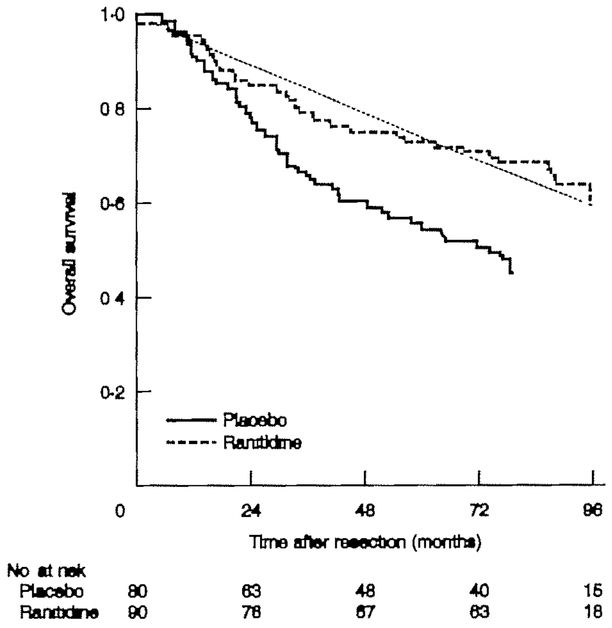

Fig. 5 Overall survival of 170 patients who had curative resection of primary colorectal cancer and were randomized to receive ranitidine or placebo, and who did not receive a perioperative blood transfusion and did not develop postoperative infectious complications. The dotted line represents the death rate of an age- and gender-matched cohort of the Danish population. Hazard ratio 0·6 (95 per cent confidence interval 0·4 to 0·9); $P = 0·01$ (log rank test)

(*Fig. 5*). Owing to the small number of patients ($n = 32$) a separate analysis was not performed in the group who did not receive perioperative blood transfusion but developed postoperative infectious complications. Furthermore, because of the association between perioperative blood transfusion and postoperative infectious complications a separate analysis was not performed for all patients with infectious complications.

To clarify the potential beneficial effect of ranitidine on survival a multivariate statistical analysis was performed on the subgroup of patients who underwent curative resection ($n = 560$). The analysis included Dukes' stage of disease, age, gender, tumour location, development of postoperative infectious complications, perioperative transfusion with blood components, and the separate group of patients who did not receive blood transfusion and did not develop postoperative infectious complications. The model considers interaction terms for no transfusion and no infection ($n = 170$), transfusion with no infection ($n = 238$), no transfusion with infection ($n = 32$) and transfusion with infection ($n = 120$). The analysis (*Table 1*) showed that tumour location in the rectum ($P < 0·001$), age at study entry ($P < 0·001$) and male sex ($P = 0·005$) were independently related to poor survival. Furthermore, ranitidine had an independent survival benefit in the subgroup of patients who did not receive perioperative blood transfusion and did not develop postoperative infectious complications (HR 0·6 (95 per cent c.i. 0·4 to 1·0), $P = 0·04$).

Discussion

The immunomodulatory effects of H_2-receptor antagonists are well established[1,6]. Perioperative treatment with these drugs reduces or inhibits operation- and blood transfusion-induced impairment of the immune response[1,6]. Moreover, ranitidine treatment was shown to improve antibody synthesis to vaccination in patients with leukaemia[27] and in patients undergoing major surgery[28]. Ranitidine also significantly improved certain immune responses in patients with HIV infection[29]. Based on detailed experimental and clinical studies[1] it has been suggested that H_2-receptor antagonists exert their immunomodulatory effects through improvements in lymphocyte responses[1]. Therefore, these drugs were expected to improve long-term survival in patients with solid tumours[6]. Furthermore, the recent demonstration of histamine and its receptor antagonists as modulators of angiogenesis[19] has restimu-

Table 1 Multivariate analysis of 560 patients who had macroscopic curative resection of primary colorectal cancer, including Dukes' stage of disease, age, gender, tumour location, perioperative blood transfusion and infectious complications

Co-variate	Hazard ratio	*P*
Dukes' stage		
A	1·0	
B *versus* A	1·7 (1·1, 2·7)	0·003
C *versus* A	3·8 (2·5, 5·8)	< 0·001
Age (years)	1·5 (1·3, 1·6)*	< 0·001
Gender (male *versus* female)	1·4 (1·1, 1·7)	0·005
Location (rectal *versus* colonic cancer)	1·5 (1·2, 1·9)	< 0·001
(−T −I) *versus* (+T +I)	0·7 (0·5, 1·1)	0·15
Ranitidine *versus* placebo in (−T −I) subgroup	0·6 (0·4, 1·0)	0·04
(+T −I) *versus* (+T +I)	0·7 (0·4, 1·0)	0·04
Ranitidine *versus* placebo in (+T −I) subgroup	1·0 (0·7, 1·4)	0·90
(−T +I) *versus* (+T +I)	0·7 (0·4, 1·4)	0·29
Ranitidine *versus* placebo in (−T +I) subgroup	1·4 (0·6, 3·4)	0·45
(+T +I)	1·0	
Ranitidine *versus* placebo in (+T +I) subgroup	0·9 (0·6, 1·4)	0·61

Values in parentheses are 95 per cent confidence intervals. *Hazard ratio per 10-year increment. Ten patients with Dukes' 'D' disease who underwent radical resection are included in the group of patients with Dukes' C disease. +T, perioperative blood transfusion; +I, development of postoperative infectious complications; −T, no perioperative blood transfusion; −I, no postoperative infectious complications

lated interest in the potential role of H_2-receptor antagonists in treatment of malignant and other angiogenesis-dependent diseases.

A comparison between ranitidine and placebo showed that ranitidine had no effect on survival of the overall population of 740 patients, or in the subgroup of 560 patients who had curative resection. The survival curves appeared to separate 3 years after the primary operation (*Figs 1* and *2*), but it is not known whether this occurred by chance or represents a small, but real, survival benefit. Patients randomized to receive ranitidine received 150 mg twice daily in the present study, half the dose used in previous clinical studies that showed beneficial effects of ranitidine[1,27–29]. Treatment with angiogenesis inhibitors does not cure patients with malignant disease, and therefore sustained treatment may prolong the asymptomatic phase, in particular after curative resection[19,30]. New studies, including higher doses than that used in the present study, are required to confirm the potential improvement in survival.

Results from recent studies have suggested that prognosis after resection of solid tumours, including colorectal cancer, is dependent on certain clinical variables in addition to disease stage. Perioperative blood transfusion and the development of postoperative infectious complications appear to identify patients with a poor prognosis[23,31,32]. These findings are supported by the observation that intraoperative and postoperative bacterial contamination can lead to increased angiogenesis[22,33]. This effect may be amplified by transfusion with blood components that include large amounts of soluble angiogenesis-stimulating molecules[21,22]. The frequency of postoperative infectious complications is significantly related to perioperative blood transfusion[23], which may explain why beneficial effects of ranitidine were not observed in patients who received perioperative blood transfusion, in contrast to the prolonged survival observed in patients who did not receive perioperative blood transfusion. Multivariate statistical analysis, including Dukes' stage of disease, tumour location, age and gender, postoperative infectious complications and blood transfusion in curatively resected patients, showed that ranitidine improved survival in patients who did not receive a blood transfusion and did not develop postoperative infectious complications. This finding was independent of Dukes' stage, tumour location, age and gender.

Histamine and its receptor blockers may participate in a concerted regulation of angiogenesis[19,34], since histamine may lead to synthesis and release of vascular endothelial growth factor (VEGF)[34]. The mechanism leading to histamine-induced VEGF release appears to be via binding to H_2 receptors, as only H_2-receptor antagonist reduces VEGF release stimulated by histamine[34]. However, VEGF release may be stimulated by a variety of other molecules and antigens[33,35], factors that are predominant after blood transfusion and infectious complications[35]. Therefore, ranitidine may preferentially exert its beneficial role as an inhibitor of angiogenesis in patients who have not received blood transfusion and who have not developed infectious complications. It remains to be established whether H_2-receptor antagonists have additional beneficial effects when used in combination with chemotherapy[36,37] or with total mesorectal excision in patients with rectal cancer.

In conclusion, the present results from a retrospective analysis of a prospective randomized study support the hypothesis that ranitidine may have a beneficial effect on survival after curative resection of colorectal cancer in patients who did not receive perioperative blood transfusion and who did not develop postoperative infectious complications.

Acknowledgements

The authors thank the staff of the Departments of Surgery, Anaesthesiology, Pathology, Clinical Biochemistry and Clinical Immunology, and blood banks of the participating hospitals for their skilful work during the study.

The study received financial support from the Danish Cancer Society (97 100 21 and 99 100 21 to H.J.N.), the Copenhagen Hospital Corporation, the Danish Pharmacy Foundation of 1991, the Ingeborg Roikjer Foundation, the Aage and Johanne Louis-Hansen Foundation, the Velux Foundation, the Hartmann Brothers Foundation, the Sophus and Astrid Jacobsen Foundation, the Hede Nielsen Family Foundation, the Kornerup Foundation, the Agnete and Poul Friis Foundation, the Trock-Jansen Family Foundation and the Leo Foundation. Glaxo Group Research Ltd, Greenford, UK sponsored the study until its discontinuation in 1996.

The Danish Ranx05 Colorectal Cancer Study Group included Svend Schulze, Jens Thorup, Peer Wille-Jørgensen and Bo Vennits (Bispebjerg Hospital), Erik Bentzen (Bornholm Hospital), Torben Pedersen, Peter Møller and the late Jens Georg Stage (Frederiksberg Hospital), Lars Banke and Dorethe Froberg (Frederikssund Hospital), Finn W. Henriksen and Poul Crone (Gentofte Hospital), Peter Hesselfeldt, Bo Hempel Sparsø and Karin Lindorff-Larsen (Glostrup Hospital), Torsten Asmussen and Jørgen Heiner (Helsingør Hospital), Ole Hart Hansen, Henrik Flyger and Peer Jess (Hillerød Hospital), Jørgen Iversen and Jørgen La-Cour Andersen (Holbæk Hospital), Janne H. Hammer and Ulla Hansen (Hvidovre Hospital), Anders Fischer and Hanne Galatius (Hørsholm Hospital), Lars Naver (Kalundborg Hospital), Dorthe Teilum (Køge Hospital), Leif Holbraad (Nykøbing F. Hospital), the late Ole Iversen, Jens Nymark and Ole Roikjær (Næstved Hospital), Leif Palm and Kirsten C. Rasmussen (Roskilde Hospital), Jørn Friis, Henrik Ovesen, Klaus Wiboltt and Charlotte Lanng (Slagelse Hospital, Lars Bo Svendsen and Lars Vedel (State (National) Hospital), Niels C. Jensen and Niels Hoffman (Stege Hospital), Torben Larsen, Jørn Packler and Peter G. Lund (Sundby Hospital).

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Lateral mucosal advancement anoplasty for anal stricture

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Presented to the annual meeting of the Pennsylvania Society of Colon and Rectal Surgeons, Philadelphia, Pennsylvania, May 2001

Paper accepted 28 June 2002

Introduction

Anatomic anal stenosis is an uncommon disabling condition. It is defined as an abnormal narrowing of the anal canal due to contracture of the epithelial lining which, to a varying extent, has been replaced by fibrous connective tissue[1]. The causes of anal stenosis include surgery of the anal canal, trauma, inflammatory bowel disease, radiation therapy, venereal disease, tuberculosis and chronic laxative abuse. Patients with congenital senile involutional stenosis have also been described[1]. Patients with anal stenosis complain of constipation, decreasing calibre of stool, difficulty in initiating evacuation, incomplete evacuation, tenesmus or bleeding.

Diagnosis is based on history and physical examination. The inability to perform a digital rectal examination or insert a standard-sized anal retractor, and the presence of anal fissures, are the most important features. Different approaches exist for the surgical treatment of anal stenosis. They include partial internal sphincterotomy and stricture release with various advancement and rotational flaps involving skin, mucosa, or both[1–5]. The surgical approach depends on the extent of stenosis as it may involve the skin, transitional zone to the dentate line, anal canal, or all of these. This study was performed to evaluate the complication rate and recurrence of anal stenosis in patients who underwent mucosal advancement anoplasty for the indication of stenosis of the skin and/or the transitional zone only.

Patients and methods

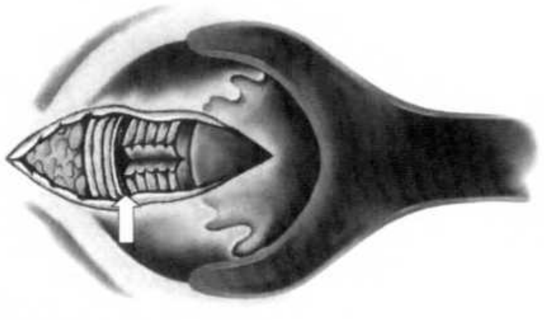
Medical records were reviewed at the authors' institution for 95 patients who underwent lateral mucosal advancement anoplasty for distal anal stricture between 1 January 1981 and 31 December 1999.

The procedure is performed on an outpatient basis using local anaesthesia following conscious sedation provided by an anaesthetist. The operation involves excision of the perianal and transitional zone scar with underlying internal sphincterotomy from the dentate line to the intersphincteric groove only. The mucosa is mobilized proximally and advanced distally to the previously noted intersphincteric groove to avoid ectropion (*Fig. 1*). The exterior wound is left open to heal by secondary intention.

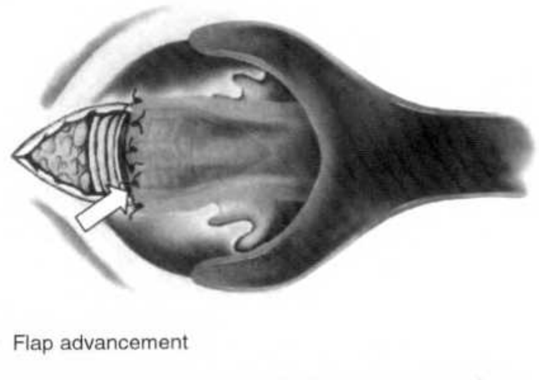
Depending on the degree of stenosis, patients initially underwent either unilateral (59 patients; 62 per cent) or bilateral (36 patients; 38 per cent) anoplasty. The complication rate and reappearance of a clinically significant anal stricture requiring reoperation during the study period (to 31 December 2000) was the measured outcome. Thirteen patients with a follow-up of less than 6 months were excluded from the analysis for restenosis. Patients were followed after operation until the wounds healed. An attempt was made to follow each patient annually.

Results

There were 40 men and 55 women with a mean age of 68 years. Mean follow-up was 50 (range 1–214) months. Only 60 patients (63 per cent) had had previous anal



a Sphincterotomy



b Flap advancement

Fig. 1 **a** Scar excised with internal sphincterotomy to the intersphincteric groove. **b** Mucosal advancement to the intersphincteric groove (arrow) without tension surgery: 35 haemorrhoidectomies, ten operations for anal fissure, four for fistula, one transanal excision of a neoplasm, and ten other miscellaneous operations.

All patients were followed after discharge for a mean of 72 days. One patient had unrecognized Bowen's disease. The overall complication rate was 3 per cent (n = 3). One patient developed an abscess and two had seepage of liquid stool, one of whom improved with time and dietary measures. Of 82 patients evaluated for the development of a restenosis that required operation, two developed recurrence in the first year, and two in each of the third, fourth and fifth years of follow-up (n = 8). Reoperation was performed in eight (10 per cent) of 82 patients for restenosis that was unresponsive to conservative management: two of 49 patients after unilateral anoplasty and six of 33 after bilateral anoplasty. Four patients with transient stenotic symptoms responded to non-operative treatment.

Discussion

The majority of surgical procedures for the treatment of distal anal and anal canal stenosis involve excision of the scar, partial internal sphincterotomy, and reshaping of the transitional zone and perianal skin with skin advancement flaps of various configurations, such as Y–V, V–Y, island, house and rotational[1–5]. These procedures result in eventual healing, but most require preoperative bowel preparation, hospital stay, general anaesthesia and extensive perianal dissection with multiple suture lines.

Flap necrosis from loss of vascular supply, suture line dehiscence from excessive suture line tension, donor site problems, local sepsis, ischaemic contracture of the leading edge of the Y-V flap, urinary tract infection, faecal incontinence and restenosis are possible complications of skin advancement flaps[1–4]. These complications are more likely following complex surgery for anal canal stenosis. A simpler technique is used for a more distal stenosis.

Martin[5] initially described the use of mucous membrane for the treatment of simple anal stricture in 1944. The Martin procedure describes a posterior midline incision and advancement of the mucosal flap over the internal sphincter following excision of the scar tissue and sphincterotomy. The internal sphincterotomy corrects the distal stenosis, and covering the distal portion of the anal canal with mucosa prevents scar reformation. Sphincterotomy is performed judiciously to avoid incontinence and extends from the dentate line to the intersphincteric groove. In patients with stenosis, this division usually includes overlying scar tissue with varying degrees of internal sphincterotomy. Despite the absence of fissure in some of these patients, this sphincterotomy widens the anal canal and the extent predicts the success of the operation. Khubchandani[2] described a lateral incision to avoid the risk of a keyhole deformity. The risk of mucosal ectropion is minimized by advancing the mucosa to, but not beyond, the distal border of the internal sphincter (intersphincteric groove). No cases of ectropion were encountered during follow-up in the present study; a bilateral repair was used if a medium to large anal retractor did not fit easily in the anal canal following unilateral repair. In the present series, eight (10 per cent) of 82 patients developed restenosis that necessitated reoperation during the follow-up period. These results were achieved with a postoperative complication rate of 3 per cent. No flap separation, necrosis or donor site dehiscence, complications that are associated with skin advancement flaps, was encountered. No postoperative urine retention or urinary tract infection was reported.

Patients with severe distal anal stenosis who initially required bilateral anoplasty appeared to be at a higher risk of subsequent restenosis (six of 33 *versus* two of 49 patients) due to the severe nature of the presenting disease. No cases of restenosis were noted after 5 years. Periodic digital self-dilatation or sequential dilatation in the clinic with Hegar dilators can be performed after operation in an attempt to avoid reoperation. Four patients responded to this method of non-operative therapy. Symptomatic distal restenosis unresponsive to conservative therapy may be managed with a contralateral mucosal advancement flap (if previously unilateral) or with skin advancement flaps.

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Original article

Salvage abdominoperineal resection in anal epidermoid cancer

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Background: In the management of isolated locoregional failure after (chemo)radiation therapy for anal epidermoid cancer, salvage abdominoperineal resection (APR) is the treatment of choice. The results of a 15-year consecutive population-based series are reviewed.

Methods: Details of all patients with anal epidermoid cancer treated from 1985 to 2000 in the Stockholm Health Care Region were recorded prospectively. Among 308 patients with biopsy-proven anal epidermoid cancer, there have been 39 isolated locoregional failures after sphincter-preserving therapy. Thirty-five patients have undergone salvage APR. The medical records of these 35 patients were reviewed retrospectively with regard to surgical and oncological results.

Results: There were no postoperative deaths. There was considerable morbidity related to the perineal wound, with postoperative perineal infections in 13 patients and delayed healing beyond 3 months in 23 patients. Complications unrelated to the perineal wound were found in 13 patients. The crude 5-year survival rate for the 35 patients was 52 per cent (median follow-up 33 months). Patients with persistent disease fared significantly worse than those with locoregional recurrence (crude 5-year survival rate 33 *versus* 82 per cent; $P < 0.05$, log rank test).

Conclusion: Salvage APR in anal epidermoid cancer is associated with a high complication rate but may result in long-term survival.

Paper accepted 28 June 2002

British Journal of Surgery 2002, **89**, 1425–1429

Introduction

Non-surgical sphincter-preserving therapy is the primary therapeutic option in patients with anal epidermoid cancer. However, for patients who have received radiotherapy or chemoradiotherapy and who present with persistent disease or recurrent locoregional failure, salvage abdominoperineal resection (APR) remains the treatment of choice[1]. A few studies have presented the outcome for patients with locoregional failure after non-surgical therapy[2–8]. Patient numbers are generally small and most series are heterogeneous. Reported survival rates at 5 years range between 23 and 45 per cent.

The Swedish National Care Programme for Anal Cancer (SNCPAC) was introduced in 1984. The treatment principles and therapeutic results of this programme on a national basis have been published previously[9]. In 1999 the Nordic Anal Cancer Programme (NOAC) replaced SNCPAC. Primary treatment recommendations are generally external-beam irradiation with or without chemotherapy. Only in small (less than 1 cm), well differentiated tumours, preferentially of the anal margin, is surgery alone considered an option in primary treatment. After an initial radiation dose of 40–46 Gy, patients are evaluated with regard to response. If complete or nearly complete tumour regression is achieved, radiotherapy is continued to a total dose of 64 Gy. If tumour response is questionable at 40–46 Gy, patients are advised to undergo an APR.

For tumours that are larger than 4 cm and/or lymph node positive, the SNCPAC originally prescribed chemoradiotherapy with 5 mg bleomycin given subcutaneously 1 h before radiation in 18 fractions. A modification of the SNCPAC protocol was implemented in Stockholm and elsewhere, from late 1989, in which this group of patients received neoadjuvant platinum (carboplatin or cisplatin) and 5-fluorouracil chemotherapy followed by radiotherapy[10]. From this period bleomycin was phased out of the treatment schedule. This regimen is now one of the treatment options in the NOAC. Evaluation following treatment includes clinical examination and biopsy from suspicious areas only. Locoregional failures with no evidence of distant metastasis are considered for salvage APR.

The aim of this study was to review the results of salvage surgery in a population-based series treated prospectively in accordance with defined protocols in a single institution.

Patients and methods

In the Stockholm Health Care Region (population 1·9 million) treatment of anal epidermoid cancer is centralized to the Oncology Department at Stockholm Söder Hospital, Huddinge University Hospital (non-surgical treatment) and the Centre of Gastrointestinal Disease, Ersta Hospital (surgery). Between January 1985 and December 2000, 308 patients with biopsy-proven invasive anal epidermoid cancer were diagnosed in the Stockholm area. All cases have been recorded prospectively. Median age at diagnosis was 70 (range 28–95) years and 241 patients (78 per cent) were women.

Of the 308 patients, 276 (90 per cent) were treated with curative intent. Fifty-two patients treated with curative intent received 50 Gy or less (range 0–50 Gy, median 45 Gy) – a less than curative dose. These 52 patients included nine who underwent local excision, 39 who had APR as part of the primary treatment and four patients whose treatment course was atypical. Patients who underwent APR after a radiation dose of 50 Gy or less were not included in the study because the operation was considered part of the primary treatment.

A total radiation dose of 60 Gy or more was delivered to 224 patients. Ninety-nine patients received radiotherapy alone and 125 underwent chemoradiotherapy. Of the patients treated with chemoradiotherapy, 74 were given neoadjuvant therapy and the remaining 51 patients received concomitant bleomycin (*Table 1*).

No evidence of persistent or recurrent disease has been detected in 172 (77 per cent) of the 224 patients who received at least 60 Gy (median follow-up 44 months). Thirteen patients have developed distant metastases, three in combination with locoregional failure. In 39 patients (17 per cent) treated with 60 Gy or more, isolated locoregional failure after primary radiotherapy or chemoradiotherapy was detected. Patients in whom locoregional failure was detected within 6 months of termination of radiotherapy, and who did not, therefore, have a full initial clinical response to radiotherapy or chemoradiotherapy, were classified as having persistent disease. When a full initial clinical response was achieved, but biopsies proved positive 6 months or more after radiotherapy had ended, patients were classified as having recurrent disease.

Table 1 Initial treatment of 224 patients with anal epidermoid cancer who received a radiation dose of 60 Gy or more

	No. of patients
Radiotherapy	99 (44)
Radiotherapy plus bleomycin	51 (23)
Neoadjuvant chemotherapy plus radiotherapy	74 (33)
Carboplatin plus 5-FU	63 (28)
Cisplatin plus 5-FU	11 (5)

Values in parentheses are percentages. 5-FU, 5-fluorouracil

Two patients with isolated locoregional failure had salvage therapy in the form of local excision. One patient died from the disease after 2 months, whereas the other is alive with no evidence of disease more than 60 months after the local excision. Two patients with isolated locoregional failure received only palliative care and died from the disease. Salvage APR was performed in 35 patients; their medical records were reviewed retrospectively.

The study was approved by the local ethics committee.

Statistical analysis

Relationships between time for perineal healing and radiation dose delivered, type of operation and male : female ratio were examined with the χ^2 test. Survival curves were calculated from the time of salvage APR until most recent follow-up using the Kaplan–Meier method. Comparison of survival between persistent and recurrent disease was performed with the log rank test. The Cox proportional hazards model was used to examine the effect on survival of type of failure, T (tumour) stage, nodal status and age. $P < 0·05$ was considered statistically significant.

Results

Characteristics of the 35 patients who underwent salvage APR are listed in *Table 2*. One surgeon participated in 30 of the 35 procedures, and a second surgeon in six. In only four cases was neither of these two surgeons part of the operating team. The median delivered radiation dose was 64 (range 60–69) Gy. No patient received postoperative chemotherapy, except after secondary recurrence following salvage APR.

Surgical results

All 35 patients underwent APR. In addition, 12 women had a partial posterior colpectomy and two men had a partial prostatic resection. An omentoplasty was performed in three patients. There was no postoperative mortality, although one patient suffered a postoperative myocardial infarction and died 4 months after operation.

Primary closure of the perineal wound was performed in 26 patients, and the other nine patients had their wounds

Table 2 Pretreatment characteristics and treatment modalities of salvage abdominoperineal resection in 35 patients

	All patients ($n = 35$)	Persistent disease ($n = 21$)	Recurrence ($n = 14$)
Median (range) age (years)	72 (39–89)	72 (42–89)	66 (39–79)
Sex ratio (M : F)	9 : 26	5 : 16	4 : 10
Tumour location			
Anal margin	5	1	4
Anal canal with or without margin	30	20	10
Histology			
Keratinizing squamous	11	5	6
Non-keratinizing squamous	7	6	1
Squamous unspecified	7	4	3
Basaloid	9	5	4
Mixed basaloid and squamous	1	1	0
Clinical stage*			
T1	6	1	5
T2	16	9	7
T3	11	9	2
T4	2	2	0
N^-	31	18	13
N^+	4	3	1
Treatment modality before APR			
Radiotherapy	12	6	6
Radiotherapy plus bleomycin	15	8	7
Neoadjuvant chemotherapy plus radiotherapy	8	7	1
Carboplatin plus 5-FU	8	7	1
Cisplatin plus 5-FU	0	0	0

*Union Internacionale Contre le Cancre tumour node metastasis (TNM) classification. APR, abdominoperineal resection; 5-FU, 5-fluorouracil

packed open. No patient had a primary muscle flap reconstruction of the perineal wound, but three patients later underwent secondary flap reconstruction because of delayed healing. Perineal wound infection that necessitated revision under general anaesthesia occurred in 13 patients. Healing time of the perineal wound exceeding 3 months was considered to be delayed, and occurred in 23 patients. In four patients the healing time of the perineal wound exceeded 1 year. Median time between termination of radiotherapy and salvage surgery was 5·8 (range 1–114) months in patients with delayed healing and 7·0 (range 2–30) months among those in whom healing was achieved within 3 months. There was no detectable difference in the radiation dose delivered, type of operation or sex ratio between the two groups.

In 13 patients complications unrelated to the perineal wound were recorded. These included small bowel obstruction (two patients), intra-abdominal abscess (one) and abdominal wound dehiscence (one), all of which required a second laparotomy. Also, there were three cases of intraoperative bleeding that required packing of the pelvis, with subsequent removal of the packing via a second laparotomy the following day. Complications not necessitating further surgical intervention included pneumonia, abdominal wound infection and peptic ulceration.

Oncological results

Three of 35 resections were not microscopically disease-free. One of the patients with incomplete resection underwent surgery because of persistent disease and two patients as a result of local recurrence after radiotherapy. One patient died 3 months after resection, another after 17 months and one is alive after a follow-up of 8 months.

No patient was lost to follow-up; the median length of follow-up was 33 (range 1–176) months after salvage APR. At the time of last follow-up 15 patients were alive, of whom 13 had no evidence of disease. The median follow-up among survivors was 57 (range 8–176) months. The crude 5-year survival rate after salvage APR was 52 per cent (*Fig. 1*). Patients in whom the local failure was classified as recurrent disease had a significantly better crude 5-year survival rate after salvage APR than those with persistent disease (82 *versus* 33 per cent; $P < 0{\cdot}05$, log rank test) (*Fig. 2*). In the Cox univariate regression analysis of survival, persistent disease, T stage 3–4, lymph node positivity and age were all statistically significant, but in a multivariate model no significant correlation was obtained (*Table 3*).

There were 15 secondary failures after salvage APR, including the three with incomplete resection. Twelve of these patients had been operated on for persistent disease. Fourteen patients have suffered local failure, two in combination with distant metastasis and one with distant spread but no local failure. All but two patients with secondary failure have died, with a median survival of 19 (range 1–78) months. No patient with a secondary failure has died when disease-free.

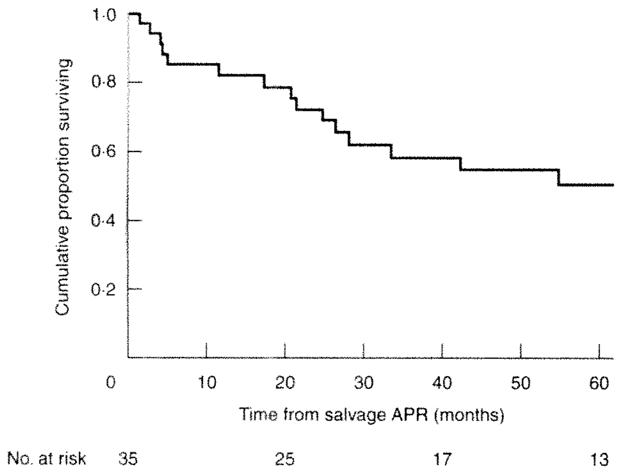

Fig. 1 Overall survival after salvage abdominoperineal resection (APR)

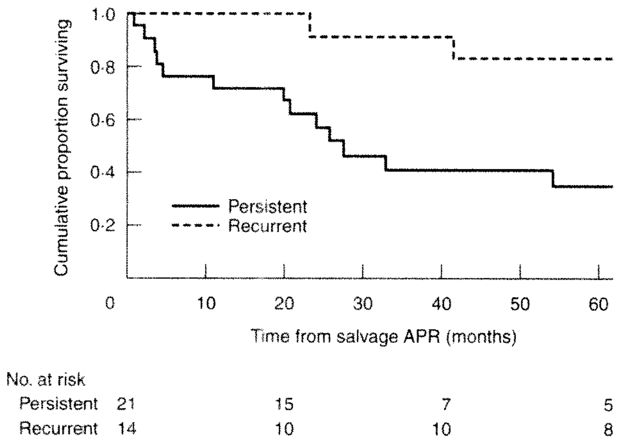

Fig. 2 Survival after salvage abdominoperineal resection (APR) in patients with recurrent and persistent disease. $P < 0.05$ (log rank test)

Discussion

APR as the sole therapeutic option in patients with anal epidermoid cancer is obsolete, but it remains the treatment of choice in those with persistent or recurrent disease after radiotherapy or chemoradiotherapy[1]. Despite progress in non-surgical treatment of anal epidermoid cancer, a substantial number of patients still demand salvage therapy. In a randomized trial with a median follow-up of 42 months, the local failure rate following full-dose radiation was 52 per cent in patients receiving radiotherapy alone and 24 per cent in those having chemoradiotherapy[11]. In the present cohort of patients, in whom chemoradiotherapy was used selectively according to defined criteria, 39 (17 per cent) locoregional failures occurred among the 224 patients who received a radiation dose exceeding 60 Gy (median follow-up 44 months).

Earlier investigators have reported 5-year survival rates after salvage APR ranging from 23 to 45 per cent[3,6–8]. In the present consecutive series, the crude 5-year survival rate was 52 per cent. Preoperative staging, meticulous technique and wide perineal excision were used, as suggested by Smith *et al.*[8], to achieve the present oncological results.

Using 6 months as a cut-off time to separate persistent disease from local recurrence is clinically relevant because evaluation of the irradiated area can be difficult several months after termination of radiotherapy. This criterion has been used previously[6]. In the present study significantly better 5-year survival was found among patients with recurrences compared with that in patients with persistent disease. These findings are consistent with those of Allal *et al.*[7], but contradict those of Pocard *et al.*[6]. The difference in survival between the two types of failure may reflect tumour stage and nodal status at initial presentation, but could also be due to differences in the responsiveness of tumours to radiation and chemotherapy, and, hence, to a more aggressive behaviour. In a report by Bonin *et al.*[12], anal

Table 3 Proportional Cox hazard regression model on survival in 35 patients

	Univariate			Multivariate		
	β	SE (β)	*P*	β	SE (β)	*P*
Type of locoregional failure (persistent, recurrent)	1·055	0·520	0·043	0·594	0·596	0·319
Tumour stage (T3–4, T1–2)	0·979	0·453	0·031	0·431	0·515	0·402
Nodal status (N^+, N^-)	1·621	0·732	0·027	1·234	0·741	0·096
Age (years)	0·040	0·019	0·031	0·029	0·019	0·131

SE, standard error

cancers with overexpression of p53 showed a trend towards worse local control following chemoradiotherapy. Also, lack of p21 expression in anal cancer has been associated with a shorter overall survival[13]. These observations are indications of biological properties of the tumour associated with response to irradiation.

Assessment of the complication rate was hampered by the retrospective nature of the study. However, delayed healing of the perineal wound is a well known complication of salvage APR in patients who have received radiotherapy. Previous authors have reported perineal wound complication rates ranging up to 30 per cent[3,6,7]. Also, in rectal cancer, preoperative radiotherapy, whether given in 5-Gy fractions or using conventional 1·8–2-Gy fractions, increases the risk of perineal wound infection with delayed healing[14]. It is likely that the high rate of delayed healing beyond 3 months reported in the present study (23 of 35) could be reduced by the increased use of omentoplasty and, in selected cases, primary muscle flap reconstruction[15,16]. The finding of a substantial complication rate unrelated to the perineal wound (13 of 35), including a second laparotomy in seven patients, is in agreement with earlier reports[6,7]. In a single-institution study of 155 APRs, mainly for adenocarcinoma of the rectum, in which only 14 per cent of patients had received preoperative irradiation, an overall morbidity rate of 23 per cent was reported[17]. Since the initial treatment – and radiotherapy in particular – renders patients more susceptible to postoperative complications, methods for the early identification of patients at high risk of local failure should continually be sought, thereby reducing the need for salvage surgery.

In conclusion, salvage APR after radiation therapy or chemoradiotherapy was associated with a high complication rate but yielded long-term survival in 52 per cent of patients.

Acknowledgements

This work was supported by the Public Health and Medical Service Committee of Stockholm County Council and by the Swedish Cancer Society.

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Clinical impact of false-negative sentinel node biopsy in primary breast cancer

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Background: The aim was to assess the false-negative sentinel node biopsy rate in women with early breast cancer and its implications in patient treatment.
Methods: Between January 1995 and March 2001, 328 consecutive patients with clinically lymph node-negative primary operable breast cancer underwent lymphatic mapping and sentinel node biopsy using a combination of preoperative lymphoscintigraphy and/or blue dye. All underwent immediate axillary dissection. The intraoperative success rate in sentinel node identification, false-negative rate, predictive value of negative sentinel node status and overall accuracy were assessed. The clinical features and primary tumour characteristics for each false-negative case were reviewed.
Results: The sentinel node was identified in 285 (86·9 per cent) of 328 women. The false-negative rate was 7·9 per cent (eight of 101). Most members of the breast multidisciplinary team would have instituted adjuvant systemic therapy for six false-negative cases based on clinical features and primary tumour histology. In all, only two (0·7 per cent) of 285 women who had sentinel node biopsy may have had their management and survival prospects potentially jeopardized owing to a false-negative sentinel node.
Conclusion: The results of this study suggest that the clinical impact of a false-negative sentinel node is low.

Paper accepted 13 June 2002

British Journal of Surgery 2002, **89**, 1430–1434

Introduction

Sentinel lymph node biopsy (SNB) is an important surgical advance in the management of early breast cancer. By limiting the extent of axillary surgery while providing accurate staging of the axillary nodes, the morbidity associated with axillary dissection is likely to be reduced. Trials comparing SNB with axillary dissection in early breast cancer are under way.

An inherent problem with SNB is the false-negative rate. A number of validation studies of SNB in conjunction with axillary clearance have demonstrated a 5–10 per cent false-negative rate associated with the procedure[1–7]. Concerns have been raised regarding the clinical impact of a false-negative SNB in terms of regional recurrence and survival[8]. The concerns regarding survival are principally related to the importance of axillary lymph node status for both management and prognosis[9,10]. However, in previous studies the extent of axillary surgery had little impact on breast cancer-specific survival[11,12]. Some authors have suggested that decisions regarding adjuvant systemic therapy can be based on the histological tumour characteristics alone[13–15].

The Royal Adelaide Hospital Breast Unit commenced a prospective evaluation of SNB in early breast cancer in August 1995. The aim of the current study was to determine the false-negative rate for SNB and to assess its clinical impact on management.

Patients and methods

A consecutive series of 328 women treated for primary operable breast cancer between January 1995 and March 2001 participated in a prospective evaluation of SNB. This series included all SNB procedures performed in the unit, without exclusion of the learning curve. The study was approved by the Royal Adelaide Hospital Human Ethics Committee and written informed consent was obtained from all patients.

One hundred and sixty-one women (49·1 per cent) had an impalpable tumour detected by screening mammography and the other 167 (50·9 per cent) presented with a palpable symptomatic mass. Their median age was 60 (range 31–82) years. All patients underwent perioperative lymphatic mapping and SNB followed by immediate level II/III axillary lymph node dissection. Eligibility/exclusion criteria, lymphoscintigraphy, lymphatic mapping and the operative technique have been described previously[8,16]. Women were included who had operable invasive primary breast cancer (tumour less than or equal to 5 cm in diameter) confirmed by cytology, core or open biopsy, but with clinically impalpable axillary lymph nodes.

Lymphoscintigraphy

All patients underwent peritumoral isotope injection with ^{99m}Tc-labelled antimony sulphide colloid ('Lymph-Flo'; Royal Adelaide Hospital Radiopharmacy) on the morning of the day of surgery. In the first 82 patients, 0·5 ml of tracer was injected. The volume was increased to 4 ml in four divided doses for the remaining patients. After injection, serial anterior and lateral images were obtained with a large-field-of-view γ camera (GE XRT; General Electric, Milwaukee, Wisconsin, USA) at 15-min intervals until a sentinel node was detected. Appropriate surface projections were marked.

Intraoperative lymphatic mapping

For the first 19 procedures, blue dye alone was used for intraoperative lymphatic mapping with the guidance of the lymphoscintigram markings. On induction of anaesthesia 1–2 ml 2·5 per cent Patent Blue V dye (Guerbet Laboratories, Villepente, France) was injected around the periphery of the tumour, which was then massaged for a minimum of 5 min.

Fifty-six women underwent lymphatic mapping using an intraoperative probe (RMD CTC 4 with audible guidance system; Gammasonics, Melbourne, Victoria, Australia) alone. This resulted in a lower intraoperative sentinel node detection rate[16], so the remaining 253 women underwent lymphatic mapping using the combined technique of blue dye and radioisotope with intraoperative probe. All blue and/or hot lymph nodes were removed intraoperatively before completion axillary dissection.

Histopathology

The pathological examination of all specimens was carried out using standard methods. Data regarding tumour size, type, grade, vascular invasion, presence and type of an *in situ* component, and clearance from surgical margins were recorded[17,18]. The expression of oestrogen (M7047; Dako, Copenhagen, Denmark) and progestogen (M3569; Dako) receptors, and the MIB-1 proliferative index (2917M; BioGenex, San Ramon, California, USA) were evaluated using immunohistochemistry. Oestrogen or progesterone positivity was defined as the presence of nuclear staining for the antibody in at least 10 per cent of the tumour cells.

The sentinel nodes were submitted in their entirety for histological evaluation. In the initial phase of the study (1995–1998) the sentinel nodes were submitted whole and bisected if larger than 1 cm. At least one haematoxylin and eosin-stained section of each node was examined. Where haematoxylin and eosin-stained sections were suspicious for metastatic tumour deposits, immunohistochemical analysis was performed using antikeratin antibody (CAM 5·2; Becton Dickinson, San Jose, California, USA). After 1998 all sentinel nodes were serially sectioned into 1–2-mm slices and at least three haematoxylin and eosin-stained sections of each node were examined, together with at least one immunohistochemical stain for cytokeratin (CAM 5·2).

For non-sentinel axillary nodes, the axillary fat was first fixed in formalin. After clearance in Carnoy's solution the lymph nodes were dissected and each node was placed in an individual cassette. Larger nodes were sliced before being embedded in paraffin. At least one haematoxylin and eosin-stained section of each node was examined.

False-negative sentinel nodes

A patient was considered to have a false-negative sentinel node when there was no histological or immunohistochemical evidence of tumour when other (non-sentinel) axillary node(s) contained metastatic tumour. Based on this, the false-negative rate, overall accuracy and predictive value of a negative sentinel node were determined.

Management planning

The clinical features and histological characteristics of the primary tumours in women with false-negative SNBs were assessed by a group of medical oncologists, radiation oncologists and breast surgeons who comprised part of the Royal Adelaide Hospital Multidisciplinary Team. In general, recommendations regarding adjuvant systemic therapy are based on consensus; patients with excellent prognostic tumour characteristics (based on the Nottingham Prognostic Index[19,20]) are not usually recommended adjuvant systemic therapy. For the purposes of this study, each member was requested to give an individual recommendation regarding the use of adjuvant systemic therapy for each woman with a false-negative SNB, assuming negative axillary lymph node status. The multidisciplinary team members were approached individually and were not aware that they were making decisions on false-negative SNBs at the time of their recommendations. Four breast surgeons, five medical oncologists and three radiation oncologists were consulted. This last part of the study was carried out retrospectively once the false-negative cases had been identified.

Results

The sentinel node was identified at the time of surgery in 285 (86·9 per cent) of 328 procedures. One hundred and one women were found to have axillary nodal metastases. Eight patients had a histologically negative sentinel node in the presence of positive non-sentinel nodes; the false-negative rate was 7·9 per cent (eight of 101). The overall accuracy of SNB in assessing the axillary nodal status was 97·2 per cent and the predictive value of a negative sentinel node in determining negative axillary nodal status was 95·8 per cent.

The clinical features and histological characteristics of the tumour in each patient with a false-negative SNB are shown in *Table 1*. The false-negative SNBs were spread evenly throughout the series of 328 procedures, with no preponderance for any individual surgeon; 12 surgeons were involved in the series. The eight false-negative SNBs were done by six different surgeons who at the time of their false-negative result had performed and/or witnessed a minimum of 30 SNB procedures.

The method of detection used in each procedure with a false-negative result and the extent of lymph node involvement is shown in *Table 2*. In three cases palpable nodal deposits were clinically evident on entering the axilla. Two patients had a previous open biopsy, while the first two patients with a false-negative SNB underwent surgery in 1997 and 1998 respectively, before a more extensive pathological examination of the sentinel node was routine. The small number of cases did not permit a statistical analysis to determine factors associated with a false-negative SNB.

When members of the multidisciplinary team were asked to evaluate each false-negative SNB, based on clinical and histological features of the primary tumour assuming negative axillary status, there was almost universal agreement to recommend adjuvant systemic therapy for six of the eight women. In two women (case E and case H), more than 75 per cent of the group recommended no adjuvant systemic therapy.

The systemic treatments that had been administered to the women with a false-negative SNB were then compared with these recommendations. Six of eight women received the same systemic treatment as recommended by the panel. The other two had been given tamoxifen, and they might have had their survival prospects jeopardized by the false-negative SNB.

Table 1 Patient and tumour characteristics in eight women with breast cancer and false-negative sentinel node biopsy

False-negative case (case no. in series)	Age (years)	Palpable mass	Histological tumour type	Tumour size (cm)	Histological grade	Vascular invasion	ER status	PR status	MIB-1 (%)*
A (20)	64	Yes	Invasive ductal	1·7	2	Absent	Positive	Positive	30
B (39)	77	Yes	Invasive ductal	2·0	2	Present	Positive	Positive	6
C (100)	47	Yes	Invasive ductal	5·5	2	Present	Negative	Negative	55
D (133)	62	No	Mixed lobular	3·0	2	Absent	Positive	Positive	9
E (160)	72	Yes	Invasive ductal	1·4	1	Absent	Positive	Positive	10
F (244)	58	Yes	Invasive ductal	2·3	1	Absent	Positive	Positive	14
G (270)	47	Yes	Invasive ductal	2·8	3	Absent	Positive	Positive	67
H (297)	72	No	Invasive ductal	0·8	1	Absent	Positive	Positive	12

*Proliferative index. ER, oestrogen receptor; PR, progesterone receptor

Table 2 Method of detection and extent of axillary involvement in eight false-negative sentinel node biopsy procedures

False-negative case	Localization used intraoperatively	Sentinel node status	No. of positive axillary nodes	No. of nodes in axillary clearance
A	Blue dye only	Blue	1	9
B	Isotope probe only	Hot	11	25
C	Blue dye + isotope probe	Hot + blue	10	18
D	Blue dye + isotope probe	Hot + blue	1	13
E	Blue dye + isotope probe	Hot only	3	19
F	Blue dye + isotope probe	Hot only	2	13
G	Blue dye + isotope probe	Hot + blue	4	20
H	Blue dye + isotope probe	Hot + blue	1	5

Discussion

The false-negative rate is an inherent problem of the technique of SNB. The reasons for this are unclear but, apart from surgical technique, may include arborization of lymphatic pathways, obstructed efferent lymphatic pathways to sentinel nodes due to tumour emboli, errors in isotope/blue dye injection or errors in histological sampling[21]. The results of the current study have demonstrated a false-negative rate of 7·9 per cent at this centre, which compares favourably with the results of other major international centres that have validated the technique of SNB with axillary clearance in breast cancer[1–7]. The eight false-negative procedures were distributed evenly throughout the series of 285 SNBs. The six surgeons had performed and/or witnessed at least 30 SNBs, and had overcome the learning phase. This suggests that surgical experience may not necessarily diminish the false-negative rate, although others have demonstrated a reduction in false-negative rate with increasing surgical experience[2–4,22].

The false-negative rate is often reported as a measure of quality assurance in SNB[7]. The false-negative rate should be calculated as the number of false-negative procedures (by virtue of a negative sentinel node in the presence of other non-sentinel axillary nodes that contain metastatic tumour deposits) divided by the sum of true-positive and false-negative cases. As such, the false-negative rate is determined principally by the rate of axillary lymph node involvement in a series. In series in which the prevalence of axillary lymph node involvement is high, one or two false-negative SNBs are likely to lead to a low false-negative rate. Conversely, in series in which smaller screen-detected tumours predominate, the prevalence of axillary lymph node involvement is low and one or two false-negative SNBs are likely to lead to an exaggerated high false-negative rate. The clinical importance of the predictive value of a negative sentinel node is rarely alluded to in validation studies. This is defined as the percentage of procedures where the sentinel node is free of metastases and the remainder of the axillary nodes are also clear. This is a useful statistic for discussion with an individual woman; in the current study the predictive value of a negative sentinel node was 95·8 per cent.

Three patients in this series had palpable, pathologically involved axillary lymph nodes at the time of axillary surgery and it may be argued that the surgeon could have chosen to complete the axillary dissection in these women. Nevertheless, for the purposes of this study these three were defined as having false-negative SNBs.

It should be remembered that standard histological assessment of axillary dissection specimens also has a false-negative rate[21,23]. Without preparation of multiple levels or immunohistochemistry this has been estimated to be in the region of 10–30 per cent. Most of the missed metastases are under 2 mm in diameter; the false-negative rate for very small metastases is higher still[21]. This has led to a more detailed examination of the axillary nodes by pathologists in this hospital since 1998. While this is time consuming and more expensive than traditional methods of examining lymph nodes, it is likely to reduce the false-negative rate of the histological technique. At this stage there is no recognized worldwide consensus on the extent of the pathological examination of the sentinel node[24]. A number of studies have shown that closer histological scrutiny of the sentinel node leads to 'upstaging'[24–26] and is likely to lead to a greater proportion of women receiving adjuvant systemic therapy.

The histological status of axillary lymph nodes is regarded as the most important prognostic determinant in early breast cancer[9,27]. However, several studies have suggested that the role of axillary lymph node status has diminished, as most decisions regarding adjuvant systemic therapy can be based on the histological characteristics of the primary tumour[13–15]. In the current study only two of the eight patients with a false-negative SNB would not have received adjuvant systemic therapy based on primary tumour characteristics. This represented less than 1 per cent of the total group of 285 patients in whom the sentinel node was identified. It is unlikely that the survival outcome of this group of patients would have been adversely affected by the false-negative SNB rate.

It is unclear, however, what effect the false-negative SNB rate may have on locoregional recurrence. Nevertheless, it is anticipated that the morbidity of axillary surgery is likely to be reduced significantly if SNB alone is performed on women with negative sentinel nodes[28,29].

It remains to be determined from the currently ongoing randomized clinical trials whether SNB is equivalent or superior to axillary dissection, the current standard in the management of the axilla. There will need to be demonstrable advantages in morbidity and disease-free survival before SNB is incorporated into clinical practice.

Acknowledgements

The authors acknowledge and thank the following medical personnel and departments for their clinical input and in preparation of the manuscript: Mr P. Malycha and Mr B. Coventry (Breast Unit, Royal Adelaide Hospital), Dr B. Chatterton (Department of Nuclear Medicine, Royal Adelaide Hospital), Professor I. Olver, Dr A. Taylor, Dr D. Keefe, Dr M. Brown and Dr T. Healy (Department of Medical Oncology, Royal Adelaide Hospital Cancer Centre), and Dr A. Muller, Dr C. Dibben and Dr S. Carruthers (Department of Radiation Oncology, Royal

Adelaide Hospital Cancer Centre); and Miss N. Bator for typing the manuscript.

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Original article

Clinicopathological analysis of early gastric cancer with solitary lymph node metastasis

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Background: The sentinel node concept has not yet been established in gastric cancer.
Methods: Fifty-four patients with early gastric cancer who had only one lymph node metastasis were regarded retrospectively as patients with a possible sentinel node metastasis, and the morphological features of these nodes were assessed. The level I nodes in seven patients with a possible skip metastasis at routine haematoxylin and eosin staining were re-examined using cytokeratin (CK) immunostaining.
Results: The shape of the gastric cancer lesion could be examined in 53 of the patients; more than one-third (20 of 53) were microfocal type. Concerning the intranodal cancer foci, the marginal sinus type was found in 32 affected nodes, medullary sinus type in 14 and mixed type in seven. Forty-three per cent of suspected sentinel nodes were the largest in size among all nodes from the station. CK immunostaining of seven non-metastatic nodes with haematoxylin and eosin revealed that three were CK positive.
Conclusion: These findings suggest that possible sentinel nodes detected by conventional means may not always be primary portions of any metastasis. Adoption of sentinel node biopsy in gastric cancer must await the development of improved procedures for diagnosis during surgery.

Paper accepted 2 June 2002

British Journal of Surgery 2002, **89**, 1435–1437

Introduction

In gastric cancer there is a growing interest in the sentinel node concept[1], which has been widely accepted in breast cancer[2–4] and malignant melanoma[5]. The feasibility and reliability of the concept have to be established with further experience of lymphatic mapping and sentinel lymphadenectomy. Lymphatic streams from the stomach wall spread in a complicated fashion[6]. It is also important to analyse the features of possible sentinel lymph nodes.

Patients and methods

Of 1381 patients with early gastric cancer (mucosal cancer, 765; submucosal cancer, 616) who underwent more than D1 lymphadenectomy from 1975 to 1998 in this hospital, 138 (10 per cent) had positive nodal metastases. Among them were 54 patients who had only one lymph node metastasis; these patients were regarded retrospectively as having possible sentinel node metastasis. The morphological features of these sentinel nodes and the primary tumours were assessed.

The shape of the nodal involvement was classified into four types[7]: macronodular, micronodular, diffuse or microfocal (*Fig. 1*). The intranodal locations of cancer foci were classified into marginal sinus type, medullary sinus type or a mixed type, according to Natsugoe *et al.*[8].

There were 45 involved sentinel nodes from level I and nine from level II (possible skip metastases) according to the classification of gastric carcinoma by the Japanese Gastric Cancer Association[9]. Level I lymph nodes in which metastatic lesions were not recognized using routine haematoxylin and eosin staining, from seven of nine patients with possible skip metastasis, were re-examined for involvement using cytokeratin (CK) immunostaining.

Results

The primary gastric cancers in patients with a solitary metastasis comprised seven mucosal cancers and 47 submucosal cancers. Histopathologically, 24 were differentiated adenocarcinoma, including papillary and tubular tumours, and 30 were undifferentiated adenocarcinoma, which included poorly differentiated, signet ring cell and mucinous tumours. Macroscopically, the gastric tumours included two elevated, 43 depressed and nine mixed-type lesions. The mean tumour size was 4·2 (range 1·3–15·0) cm.

It was possible to examine the shape of the metastases in 53 of the sentinel nodes; there were six macronodular, seven micronodular, 20 diffuse and 20 microfocal lesions. Histologically, two macronodular, seven micronodular, ten diffuse and 15 microfocal lesions were undifferentiated adenocarcinomas. With regard to intranodal cancer foci, the marginal sinus type was found in 32 affected nodes (60 per cent), the medullary sinus type in 14 (26 per cent) and the mixed type in seven (13 per cent).

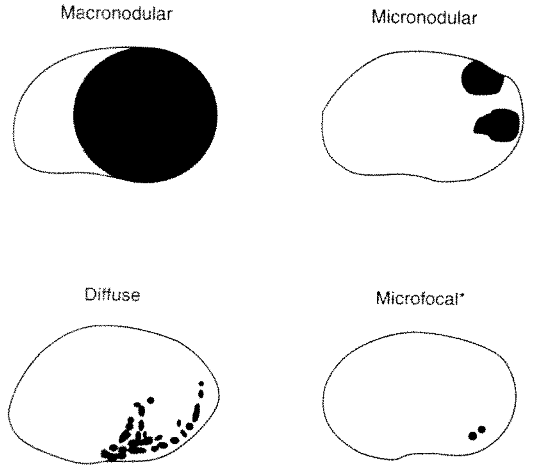

Fig. 1 Classification of the shapes of cancer involvement in metastatic lymph nodes (from reference 7). *Metastasis within a few cancer cells (or tubules)

The maximum size of the sentinel node was less than 5 mm in 33 nodes (62 per cent), between 5·1 and 10 mm in 11 nodes (21 per cent) and greater than 10·1 mm in nine nodes (17 per cent) (*Fig. 2*). The mean size was 5·9 mm and the median 4·5 (range 1·5–23) mm. The possible sentinel node was the largest of all nodes from the station in 43 per cent.

The site of the possible skip metastasis was along the left gastric artery in three tumours, along the anterior common hepatic artery in three, along the coeliac artery in one, along the proximal splenic artery in one and along the right paracardial node in one tumour. CK staining of the level I nodes from seven patients thought to have skip metastasis showed that, although all were negative on haematoxylin and eosin staining, three were CK positive.

Discussion

Many authors have validated the use of sentinel node biopsy in breast cancer[2–4]; the study is now under way for gastric cancer. Initially, the accuracy of intraoperative identification of sentinel nodes by vital dye[10] or isotope[1] has to be evaluated by comparing the pathological results of all the dissected lymph nodes. Numerous cases will be required to validate the sentinel node technique because of the low incidence of nodal metastasis in early gastric cancer and the complexity of lymphatic drainage of the stomach. In the current study, patients with a solitary lymph node metastasis, who might have had sentinel node metastasis, were evaluated in terms of the sentinel node concept by their clinicopathological features.

The following features were found: the maximum size of the possible sentinel nodes was relatively small; an involved

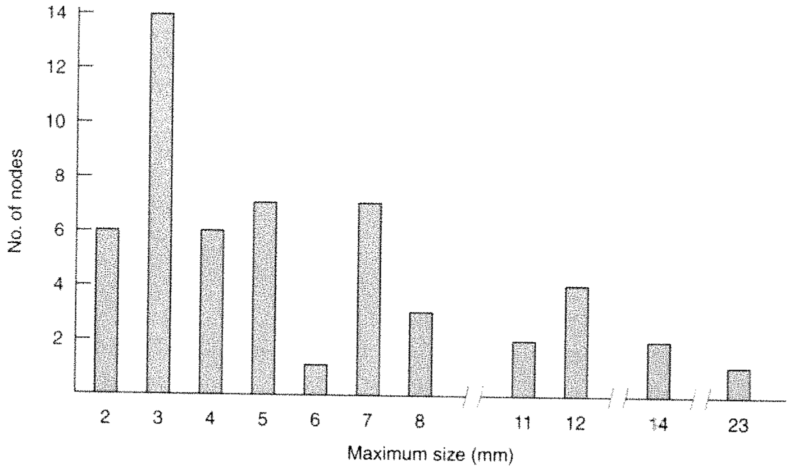

Fig. 2 Distribution of the maximum size of each metastatic lymph node

node was not necessarily the largest node in the station; the shape of intranodal cancer involvement was frequently diffuse or microfocal; intranodal cancer foci were often located at the marginal sinus; true skip metastasis was rare.

Nakamura *et al.*[11] analysed the regional lymph nodes in early gastric cancer. Consistent with the present study, the mean maximum size of lymph nodes with metastasis was 4·8 mm, and such nodes were not necessarily the largest of the dissected lymph nodes. Although Palaia *et al.*[10] considered the sentinel node to be larger than 5 mm in gastric cancer, as in breast cancer and melanoma, micrometastasis in small nodes might be overlooked.

There are limitations to frozen-section examination during surgery, particularly concerning micrometastasis, which accounts for more than 30 per cent of sentinel node metastasis. Natsugoe *et al.*[8] re-examined the lymph nodes in 57 patients with submucosal cancer, using three additional sectioning methods, and found six patients with metastasis among those thought to have no metastasis by routine staining. Siewert *et al.*[12] and Maehara *et al.*[13] noted the frequent occurrence of nodal micrometastasis identified by immunohistochemical techniques and emphasized its importance as a prognostic factor. The potential to overlook micrometastasis was verified by CK staining in three of seven patients considered to have skip metastasis in the present study. These findings suggested that sentinel nodes detected by conventional means in gastric cancer may not always be primary portions of a metastasis. Although Kosaka *et al.*[14] reported that the incidence of skip metastasis was higher than expected, overlooking of micrometastasis of level I nodes by routine staining cannot be ruled out.

It is too early to adopt sentinel node biopsy in gastric cancer until new diagnostic devices for detecting and analysing lymph node metastasis during surgery are developed.

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Original article

Value of palliative resection in gastric cancer

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Background: Western patients with gastric cancer often present with incurable disease. The role of palliative surgical resection is still debatable. Non-curatively treated patients from the Dutch Gastric Cancer Trial were studied to define more accurately which patients might benefit from palliative resection.

Methods: In the Dutch Gastric Cancer Trial 285 (26 per cent) of the randomized patients were found to have incurable tumours at laparotomy. Four signs of incurability were noted: irresectable tumour (T^+), hepatic metastasis (H^+), peritoneal metastasis (P^+) and distant lymph node metastasis ($N4^+$). Patients had either an explorative laparotomy, a gastroenterostomy, or a resection (partial or total). In the analysis, particular attention was paid to the prognostic factors of age, number of metastatic features, and a combination of these.

Results: Overall survival time was greater if a resection was performed (8·1 *versus* 5·4 months; $P < 0{\cdot}001$). For patients aged over 70 years there was still a survival advantage of about 3 months if resection was carried out. Morbidity and perioperative mortality rates in this older age group were, however, high (50 and 20 per cent respectively). For patients with one metastatic site a resection was of significant benefit (survival 10·5 *versus* 6·7 months; $P = 0{\cdot}034$). For patients with two or more metastatic sites resection had no significant survival advantage (5·7 *versus* 4·6 months; $P = 0{\cdot}084$). Combination of these factors indicates that patients aged less than 70 years with one metastatic site will benefit significantly from a palliative resection, in contrast to other combinations of factors.

Conclusion: Age as well as the number of metastatic sites should be taken into account when a palliative resection is considered. Palliative resection may be beneficial for patients under 70 years of age if the tumour load is restricted to one metastatic site.

Paper accepted 13 June 2002

British Journal of Surgery 2002, **89**, 1438–1443

Introduction

Gastric cancer is a common malignancy. In Japan it is the leading cause of death with an annual mortality rate of 90 per 100 000 population. Gastric cancer is detected much less frequently in Western countries such as the USA and the Netherlands, where annually approximately 15 people per 100 000 population die from gastric cancer. The incidence of gastric cancer in the Netherlands is about 2200 people per year (population about 17 million), and seems to be decreasing slightly[1]. Owing to this low incidence, a screening programme is not cost effective and, as a result, most patients with gastric cancer present at an advanced stage. In the Dutch Gastric Cancer Trial, 285 patients (26 per cent) were found to be incurable after randomization[2].

Surgical resection is the principal treatment for gastric cancer aimed at cure. For Western patients who cannot be cured, several studies have shown that resection may be beneficial in terms of survival[3–6], although this is strongly influenced by the extent of the tumour and metastasis[7]. This survival advantage, however, may be at the cost of increased postoperative morbidity, prolonged hospital stay and high mortality rates, and the quality of life in these patients may be reduced rather than improved[8–10].

In curative gastric cancer surgery, morbidity and mortality are greatly influenced by age[11]. For non-curative gastric cancer surgery this prognostic factor has not yet been evaluated. A study was undertaken of 285 patients who were found to be incurable after entry in the Dutch Gastric Cancer Trial, with special attention to age and the number of positive sites, in order to define more accurately which Western patients may benefit from non-curative resection.

Patients and methods

Between 1989 and 1993, 1078 patients with histologically proven gastric cancer were randomized in the Dutch Gastric Cancer Trial to undergo gastric resection with either a D1 (limited) or a D2 (extended) lymph node dissection. Patients had no signs of distant metastasis at clinical examination, chest radiography and liver ultrasonography. Computed tomography and laparoscopy were not used routinely for staging gastric cancer in the Netherlands at the time of the trial. Other entry criteria have been described previously[12]. Of 1078 randomized patients, 996 were eligible for the study[2].

In concordance with the criteria of the Japanese Research Society for the Study of Gastric Cancer (JRSGC)[13], four sites for tumour spread were investigated at laparotomy. Patients with macroscopically resectable tumour (T^-), without hepatic (H^-) or peritoneal (P^-) metastasis, and without the involvement of distant lymph nodes ($\mathrm{N4}^-$) (nodal station 16 in the JRSGC classification), confirmed by frozen section of a para-aortic lymph node biopsy, were regarded as curable and had the planned type of dissection. Cytological examination of abdominal washings was not mandatory for the trial. If there was tumour growth in neighbouring organs, but this was radically resectable, the operation was considered curative. If, however, one of these four sites was positive for tumour (T^+, H^+, P^+, $\mathrm{N4}^+$), the operation was classified as non-curative. In these cases the patient had subsequent treatment chosen by the surgeon. This could be exploration only, gastroenterostomy or gastric resection (partial or total). Based on the above criteria, 285 (29 per cent) of the 996 eligible patients were considered incurable and form the study group.

Survival, morbidity, hospital stay and hospital mortality were determined and correlated with age and extent of metastasis. Hospital mortality was defined as death within 30 days or during hospital stay. Morbidity included all complications. Hospital stay excluded hospital deaths as analysis including hospital death led to nearly exactly the same numbers. Data on quality of life and duration of intensive care unit stay were not registered in the Dutch Gastric Cancer Trial.

Statistical analysis

The Statistical Package for the Social Sciences software program (SPSS®, Chicago, Illinois, USA) was used. The χ^2 test was employed to evaluate differences in proportions and the Mann–Whitney *U* test was used to assess the significance of differences in hospital stay. The Kaplan–Meier method was used to compare mean and median survival. Statistical analysis of survival differences was done with the log rank test.

Results

Of the 285 non-curative operations, 129 patients had no resection and underwent gastroenterostomy or an explorative laparotomy only. Some 156 patients had a palliative resection. There was no difference in sex ratio or age (median 65 (range 30–86) years) between these two groups.

The overall median survival of patients who underwent palliative resection was 8·1 months, and that of those who had no resection was 5·4 months ($P < 0{\cdot}001$). Morbidity was significantly higher in the resection group (38 *versus* 12 per cent; $P < 0{\cdot}001$) and these patients had a significantly longer median hospital stay (15 *versus* 10 days; $P < 0{\cdot}001$). The mortality rate was not significantly different (12 *versus* 10 per cent respectively) (*Table 1*).

Patients over 70 years of age had a significantly higher morbidity ($P < 0{\cdot}05$) and longer hospital stay ($P < 0{\cdot}01$) compared with those aged 70 years or less. The mortality rate for patients over 70 years who had resection was also higher than that of the younger patients who had resection (20 *versus* 9 per cent), but this difference was not statistically significant ($P = 0{\cdot}06$). If, however, the patient survived palliative resection, the median survival for the two age groups was nearly equal (*Table 1*).

Widespread tumour growth (T^+) was found in 192 patients and peritoneal metastasis (P^+) in 142. In 49 patients preoperative ultrasonography of the liver failed to detect hepatic metastasis (H^+), and in 74 peroperative para-aortic lymph node biopsy showed tumour infiltration ($\mathrm{N4}^+$). The distribution of these positive signs between the resection and no resection group were, respectively: T^+, 84 (54 per cent) and 108 (84 per cent); P^+, 59 (38 per cent) and 83 (64 per cent); H^+, 25 (16 per cent) and 24 (19 per cent); and $\mathrm{N4}^+$, 46 (29 per cent) and 28 (22 per cent). Combinations of different signs are clearly possible.

The majority of patients with widespread tumour growth (T^+) or peritoneal metastasis (P^+) did not undergo resection, whereas N4 lymph node involvement usually led to a palliative resection. One positive sign was found in 149 patients, two positive signs in 103 patients, and more than two signs in 33. Most patients with one positive sign underwent a palliative resection (105 (70 per cent) of 149), whereas patients with two or more positive signs usually had a non-resective procedure (85 (62 per cent) of 136).

For patients with one positive sign who had a resection, the median survival was 10·5 months, compared with 6·7 months for those who did not have a resection

Table 1 Morbidity, hospital stay and mortality after operation in 285 incurable patients

	No. of patients	Morbidity*	Hospital stay (days)†	Mortality*	Survival (months)	
					Median	Mean
All ages						
No resection						
Exploration	78	9 (12)	9 (3–93)	8 (10)		
Gastroenterostomy	51	7 (14)	11 (7–27)	5 (10)		
Total	129	16 (12)	10 (3–93)	13 (10)	5·4	8·0
Resection						
Partial gastrectomy	93	28 (30)	14 (7–154)	12 (13)		
Total gastrectomy	63	31 (49)	17 (11–82)	7 (11)		
Total	156	59 (38)	15 (7–154)	19 (12)	8·1	14·3
P‡		< 0·001	< 0·001	n.s.	< 0·001	
Age 70 years or less						
No resection						
Exploration	50	5 (10)	9 (3–93)	6 (12)		
Gastroenterostomy	37	4 (11)	12 (7–27)	2 (5)		
Total	87	9 (10)	10 (3–93)	8 (9)	5·4	7·9
Resection						
Partial gastrectomy	66	18 (27)	13 (7–57)	8 (12)		
Total gastrectomy	44	18 (41)	17 (11–81)	2 (5)		
Total	110	36 (33)	14 (7–81)	10 (9)	8·0	14·3
P‡		< 0·001	< 0·001	n.s.	< 0·001	
Age over 70 years						
No resection						
Exploration	28	4 (14)	10 (5–42)	2 (7)		
Gastroenterostomy	14	3 (21)	11 (8–20)	3 (21)		
Total	42	7 (17)	11 (5–42)	5 (12)	4·6	8·0
Resection						
Partial gastrectomy	27	10 (37)	16 (10–154)	4 (15)		
Total gastrectomy	19	13 (68)	24 (14–82)	5 (26)		
Total	46	23 (50)	18 (10–154)	9 (20)	8·1	14·2
P‡		0·001	< 0·001	n.s.	0·03	

*Values in parentheses are percentages. †Values are median (range); hospital deaths excluded. n.s., Not significant. ‡Resection *versus* no resection (Mann–Whitney *U* test for hospital stay, Kaplan–Meier test for survival, and χ^2 test for morbidity and mortality)

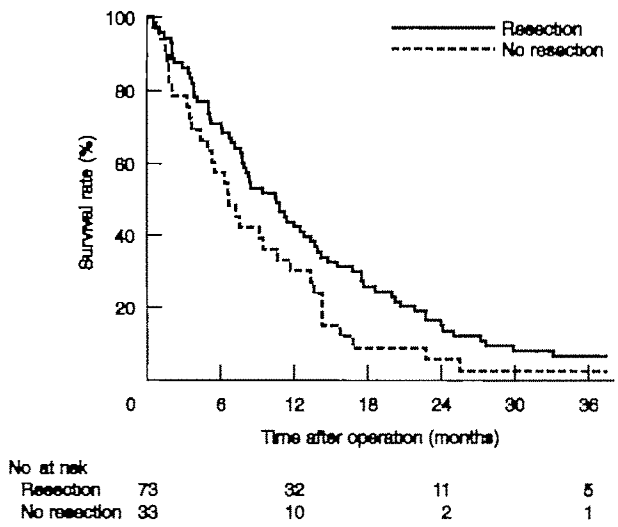
($P = 0.034$). When two or more signs of incurability were found, the survival advantage for patients who underwent palliative resection disappeared. Median survival for these patients was 5·7 months (resection) and 4·6 months (no resection) ($P = 0.084$). In a multivariate analysis there was no significant difference in survival between the four metastatic signs.

If age and number of metastatic sites were both taken into account, only the group of patients under 70 years of age with one metastatic site had a significant survival benefit following resection. All other combinations fail to show a significant survival benefit (*Figs 1–4*).

Discussion

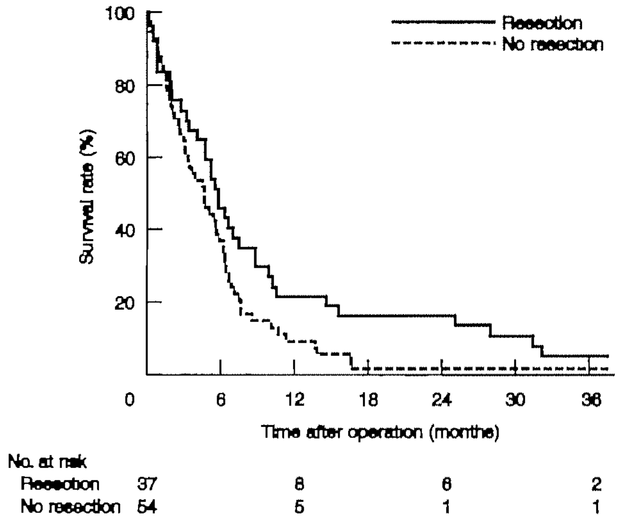
As a result of better preoperative staging of patients with gastric cancer, the proportion of patients operated on has decreased from 92 per cent before 1970 to 71 per cent in 1990. The resectability rate of gastric cancer has increased from 37 per cent before 1970 to 48 per cent in 1990. This is partly due to earlier diagnosis but also to the performance of extended operations and improved patient selection. Nevertheless, only 31 per cent of patients with gastric cancer underwent a curative resection[14]. In the Dutch Gastric Cancer Trial, 285 (26 per cent) of 1078 randomized patients were classified as incurative at laparotomy[2].

Whether patients benefit from a palliative resection is debatable. Quality of life is an important issue and strongly influenced by the adverse effects of surgery. Owing to the nature of the study, no information on quality of life was collected. Although in most Western studies palliative resection is associated with prolongation of survival[3–6], this can be at the expense of serious morbidity and high mortality rates. In the present study, the morbidity rate was 12 per cent for patients who had no resection and up to 38 per cent for those who had a resection, leading to a significant difference in median hospital stay of 10 and 15 days respectively. Although comparable to other



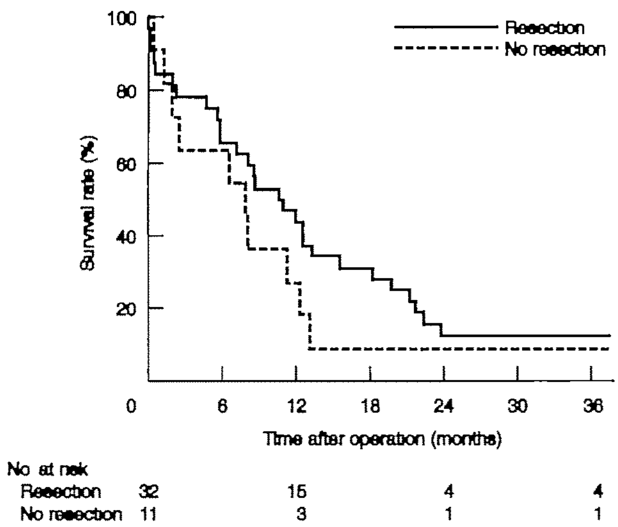
No. at risk				
Resection	73	32	11	5
No resection	33	10	2	1

Fig. 1 Survival following resection and no resection in patients aged 70 years or less and with one positive sign of incurability. $P = 0.03$ (log rank test)



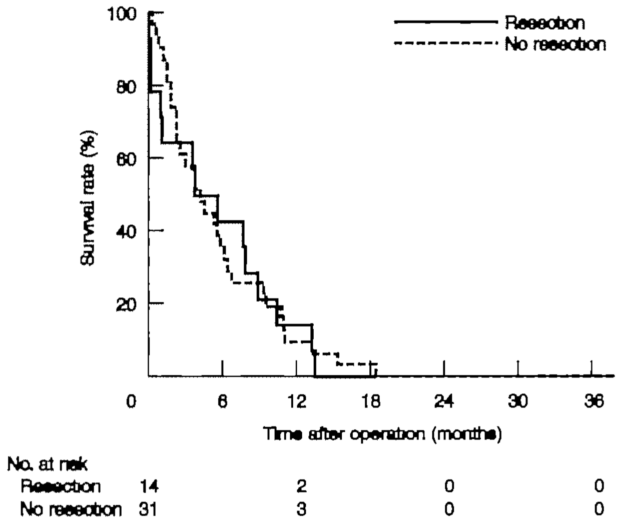
No. at risk				
Resection	37	8	6	2
No resection	54	5	1	1

Fig. 2 Survival following resection and no resection in patients aged 70 years or less and with two or more positive signs of incurability. $P = 0.07$ (log rank test)



No. at risk				
Resection	32	15	4	4
No resection	11	3	1	1

Fig. 3 Survival following resection and no resection in patients aged more than 70 years and with one positive sign of incurability. $P = 0.48$ (log rank test)



No. at risk				
Resection	14	2	0	0
No resection	31	3	0	0

Fig. 4 Survival following resection and no resection in patients aged more than 70 years and with two or more positive signs of incurability. $P = 0.82$ (log rank test)

Western studies[3,4], these are important issues that should be taken into account when considering palliative resection.

The overall mortality rate for curative resections in the Dutch Gastric Cancer Trial was 6·6 per cent[7], although elderly patients were at risk of increased morbidity and mortality[11]. If age is introduced as a prognostic factor in the palliatively treated group, it is clear that morbidity and hospital stay are significantly higher for the group over 70 years of age. The large difference in mortality nearly reached significance. With a morbidity rate of up to 50 per cent and a mortality rate of up to 20 per cent after resection, it is questionable whether elderly patients benefit from a non-curative resection.

Several Japanese studies have examined the influence of tumour load on the results of palliative surgery. Ouchi *et al.*[8] showed that a palliative resection correlated with better survival and that the extent of peritoneal involvement did have an influence on quality of life but not on survival.

Kikuchi *et al.*[15] found that the extent of peritoneal metastasis did not affect prognosis significantly, and palliative resection seemed to have a beneficial effect on the postoperative course if there was no evidence of liver metastasis.

Isosaki *et al.*[9] and Maekawa *et al.*[10] divided their patients in four groups with signs of advanced gastric cancer (T^+, H^+, P^+ and $N4^+$), as in the present study. Isosaki *et al.*[9] found a 5-year survival rate of 33 per cent for patients with a single positive sign, 10 per cent for those with two factors and 0 per cent for those with three factors. In the study of Maekawa *et al.*[10] 216 of 296 patients had a palliative resection, whereas 77 had no resection. The 5-year survival rate was 14 per cent for resected patients with one positive sign and 6 per cent for those with two signs. All patients with three or more positive signs died within 2 years. All patients who had no resection died within 1 year. Both studies[9,10] concluded that an aggressive approach could be recommended in patients with one positive sign of advanced gastric cancer, but any survival benefit disappeared with an increasing number of positive signs. In the present study there was a significant survival advantage for those who had a palliative resection, although there were no patients with long-term survival[7]. As in the above studies[9,10], patients with one positive sign had a significant survival advantage after resection, but this disappeared with two or more positive signs.

Combination of the prognostic factors of age and number of positive signs in order to select patients for palliative resection has not been described previously. This study has shown that patients under 70 years of age with one positive sign benefit from a palliative resection. For all other patients there was no survival benefit. If morbidity, hospital stay and mortality are also considered, there is probably no gain for patients aged more than 70 years undergoing palliative resection.

Acknowledgements

The Dutch Gastric Cancer Trial was supported by grants from the Dutch Health Insurance Funds Council and the Netherlands Cancer Foundation.

The authors are indebted to the participating surgeons and pathologists of the Dutch Gastric Cancer Group and to the data centre of the Department of Surgery at Leiden University Medical Centre for its contribution to this trial.

The following centres took part in the study: Medisch Centrum Alkmaar, Rijnoord Alphen, De Lichtenberg Amersfoort, Ziekenhuis Amstelveen, Academisch Medisch Centrum Amsterdam, Academisch Ziekenhuis Vrije Universiteit Amsterdam, Antoni van Leeuwenhoekhuis Amsterdam, St Lucas Amsterdam, Bovenij Amsterdam, Slotervaart Amsterdam, Gooi Noord Blaricum, Ziekenhuis Centrum Apeldoorn, Rijnstate Arnhem, Diaconessenhuis Arnhem, Wilhelmina Assen, Rode Kruis Beverwijk, St Ignatius Breda, St Gregorius Brunssum, Renier de Graaf Gasthuis Delft, Delfzicht Delfzijl, Geertruiden Deventer, Nij Smellinghe Drachten, Catharina Eindhoven, Diakonessenhuis Eindhoven, Dr Jansen Emmeloord, Scherperziekenhuis Emmen, St Anna Geldrop, Bleuland Gouda, Bronovo 's-Gravenhage, Westeinde 's-Gravenhage, Rode Kruis 's-Gravenhage, Leyenburg 's-Gravenhage, Academisch Ziekenhuis Groningen, Martini Groningen, Johannes de Deo Haarlem, Elisabeth Gasthuis Haarlem, Röpcke Zweers Hardenberg, Oranjeoord Harlingen, Spaarne Heemstede, Tjongerschans Heerenveen, Elkerliek Helmond, Streekziekenhuis Midden Twente Hengelo, Groot Ziekengasthuis 's-Hertogenbosch, Bethesda Hoogeveen, West Fries Gasthuis Hoorn, Zeeweg IJmuiden, Medisch Centrum Leeuwarden, Diaconessenhuis Leiden, Academisch Ziekenhuis Leiden, St Antoniushove Leidschendam, IJsselmeerziekenhuizen Lelystad, Academisch Ziekenhuis Maastricht, Diaconessen Inrichting Meppel, Canisius-Wilhelmina Nijmegen, Academisch Ziekenhuis Radbout Nijmegen, St Laurentius Roermond, Academisch Ziekenhuis Dijkzigt Rotterdam, St Franciscus Gasthuis Rotterdam, St Clara Rotterdam, Antonius Sneek, Ruwaard van Putten Spijkernisse, Rivierenland Tiel, St Elisabeth Tilburg, Academisch Ziekenhuis Utrecht, Diakonessen Utrecht, Overvecht Utrecht, St Joseph Veghel, St Elisabeth Venray, Streekziekenhuis Walcheren Vlissingen, Diaconessenhuis Voorburg, St Jans Gasthuis Weert, St Lucas Winschoten, Streekziekenhuis Koningin Beatrix Winterswijk, 't Lange Land Zoetermeer, 't Nieuwe Spitaal Zutphen, Sophia Zwolle, and De Weezenlanden Zwolle.

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Original article

Apoptosis in Barrett's oesophagus following antireflux surgery

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Background: Intestinal metaplasia persists in Barrett's mucosa despite control of reflux. Tissue homeostasis is maintained by the balance between apoptosis and proliferation. There is an unexplained temporary increase in proliferation in patients with Barrett's mucosa after antireflux surgery, and the long-term effect of any therapy in altering this balance remains unclear. The aim of this study was to assess apoptosis in Barrett's oesophagus following antireflux surgery.

Methods: Apoptosis was evaluated in endoscopic biopsy specimens from 19 patients with Barrett's oesophagus 4 years after Collis–Nissen gastroplasty using an *in situ* terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate–biotin nick end labelling (TUNEL) method.

Results: Intestinal metaplasia had a lower apoptosis index than gastric metaplasia (0·27 *versus* 2·14 per cent; $P < 0{\cdot}001$). After operation there was a steady increase of apoptosis in intestinal metaplasia over time (from 0·23 per cent before operation to 0·42 per cent within 2 years and to 0·59 per cent 4 years after operation; $P = 0{\cdot}015$). Patients with persistent acid exposure did not show any increase in apoptosis in comparison with patients without acid exposure (0·41 *versus* 0·59 per cent; $P = 0{\cdot}91$).

Conclusion: Apoptosis is less in intestinal metaplasia than in gastric metaplasia, although there is an increase after antireflux surgery. Persistent acid reflux may predispose to malignancy.

Paper accepted 28 June 2002

British Journal of Surgery 2002, **89**, 1444–1449

Introduction

Gastro-oesophageal reflux disease is the most common foregut disorder, affecting more than 10 per cent of the Western world population[1]. Barrett's oesophagus, the replacement of the normal squamous epithelium of the distal oesophagus by a metaplastic intestinal epithelium, is considered to be an advanced complication of long-standing gastro-oesophageal reflux[2]. It occurs in 5–10 per cent of patients with chronic gastro-oesophageal reflux and results in a 30–125-fold excess risk of developing oesophageal adenocarcinoma[3–6]. This type of oesophageal cancer has, at present, the most rapidly increasing incidence among all malignancies in North America and in some European countries[7,8]. The histological sequence of chronic gastro-oesophageal reflux–metaplasia–dysplasia–adenocarcinoma is well established[9–11]. Chronic reflux oesophagitis may be expected to predispose to cancer by increasing the turnover and proliferation of metaplastic epithelial cells.

Normally dividing cell populations maintain a balance between cell proliferation and cell loss[12,13]. Cell loss occurs by several mechanisms, including cell shedding, necrosis and apoptosis. Apoptosis is a process of programmed cell death, characterized morphologically by fragmentation of the DNA due to double-strand breaks[14]. This provides a means of disposing of senescent, DNA-damaged or diseased cells. Thus, any alteration in the proliferation to apoptosis balance can potentially play an active role in Barrett's oesophagus-associated tumorigenesis. Apoptosis is induced by cell proliferation and DNA damage, and is regulated by various modulators. Genes such as *p53*, c-*myc*, *Fas* and *ICE* (interleukin 1β-converting enzyme) are known inducers of apoptosis, whereas *bcl-2*, *ras* and *pRb* (retinoblastoma protein) are known to be repressors of apoptosis[13,15].

The authors have previously found a temporary increase in proliferation in Barrett's mucosa immediately after

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

antireflux surgery, despite control of reflux[16]. Whether this increase reflects the response to operative trauma or malignant progression in Barrett's mucosa remains unclear. This observation prompted further investigation of apoptosis in biopsy specimens in which proliferation had also been assessed. The aim of this study was to investigate the apoptotic activity of Barrett's oesophagus mucosa over a long period of time after reflux correction and to correlate this activity with cellular proliferation.

Patients and methods

Patients

Between January 1989 and December 1997, 45 patients with Barrett's oesophagus underwent a Collis–Nissen repair to control oesophageal reflux[17]. Nineteen patients completed more than 2 years of follow-up. Intestinal metaplasia was documented in endoscopic biopsies taken before operation and at 0–2 and 2–4 years after operation. These endoscopic biopsy specimens were used in the present investigation.

Endoscopy and biopsy

Endoscopic examinations were performed using a video monitoring system (Olympus® GIF-130; Olympus Canada, Toronto, Ontario, Canada). The specimens were obtained by four-quadrant multiple biopsies starting from the muscular gastro-oesophageal junction before operation, or the top of fundic wrap after operation, to the mucosal gastro-oesophageal junction at 2-cm intervals within the metaplastic mucosa. These specimens were fixed immediately in 3·7 per cent buffered formalin. Histopathological diagnosis of haematoxylin and eosin-stained sections was performed independently by two pathologists (L.G. and C.Y.H.). The diagnosis of Barrett's oesophagus was based on the presence of intestinal-type goblet cells in at least one biopsy from abnormal mucosa in the lower oesophagus, irrespective of its length. To ascertain the presence of intestinal goblet cells, Alcian blue staining was performed if there was doubt.

TUNEL immunohistochemistry

Serial sections 5 μm thick were mounted on Superfrost®/Plus glass slides (Fisher Scientific, Portsmouth, New Hampshire, USA). Apoptotic cells with fragmented DNA were detected with the *in situ* terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)–biotin nick end labelling (TUNEL) method. Sections were incubated at room temperature for 15 min in a saponin–ethylene glycol tetra-acetic acid (EGTA) (0·1 per cent) solution, washed in phosphate-buffered saline (PBS) and incubated for 30 min at 37°C in 5 × reaction buffer containing cobalt chloride 2·5 mmol/l, TdT 20 units and biotin-16–dUTP 0·5 nmol/l (Roche, Indianapolis, Indiana, USA). For the negative controls, TdT was substituted by water. Sections were rinsed in PBS and incubated for 30 min at room temperature in a stop solution consisting of 4 × saline sodium citrate (SSC) buffer and 5 per cent dried skimmed milk. Slides were then incubated for 30 min at room temperature in 4 × SSC buffer containing fluorescein isothiocyanate (FITC)-labelled ExtrAvidin® 0·06 mg/ml (Sigma, St Louis, Missouri, USA), 0·1 per cent Triton X-100™ and 5 per cent dried skimmed milk. As for the whole-cell population, all nuclei were stained by incubation for 15 min at room temperature in the presence of propidium iodide 5 nmol/l (ICN Biomedicals, Aurora, Ohio, USA). Slides were then mounted in a fluorescence-enhancing medium (VECTASHIELD®; Vector Laboratories, Burlington, Vermont, USA).

A confocal laser scanning microscope, LSM 510 (Axionvert 100M; Carl Zeiss®, Jena, Germany), equipped with both visible and ultraviolet laser modules was used for image analysis. After completing the protocol, the tissue specimens were viewed at low magnification (× 100) with a red filter (high pass 560, wavelength 543 nm for propidium iodide staining) in order to choose well oriented glandular crypts; then a high magnification view (× 400) was used to select the image showing all nuclei. Once the field had been defined, a green filter (band pass 505–530, wavelength 488 nm for fluorescence staining) was used to gain the image from the same field while showing only apoptotic cells.

Finally, the synchronization of these two images acquired with the LSM 510 was employed to calculate the apoptosis index. The apoptosis index was determined as the percentage of TUNEL-positive epithelial cells (yellow to bright green nuclei, sharply delineated spots) to the total number of epithelial cells (bright red nuclei, sharply delineated spots) per high-power field. In this way interstitial cells were excluded from the evaluation. The apoptosis index in gastric metaplastic mucosa was also calculated when appropriate. The two pathologists who evaluated the apoptosis index (C.Y.H. and L.G.) were blinded with respect to clinical information at the time of examination.

Cellular proliferation in the same specimens was also measured by these authors (L.G. and C.Y.H.), using Ki-67 immunohistochemistry, as has been described in detail elsewhere[16].

Statistical analysis

Data are presented as median (interquartile range; i.q.r.). Depending on the distribution of data, two-way analysis of variance or the Friedman test was applied as appropriate for multiple-group comparison. The grouped Student *t* test or the Mann–Whitney *U* test was used to determine differences between two groups, and the paired student *t* test or the Wilcoxon signed ranks test was applied for paired sample comparison. A two-tailed exact *P* value was presented unless it was less than 0·001. $P < 0{\cdot}05$ was considered statistically significant. The statistical analysis was performed with the Statistical Package for the Social Sciences version 7·5 for Windows® (SPSS®, Chicago, Illinois, USA).

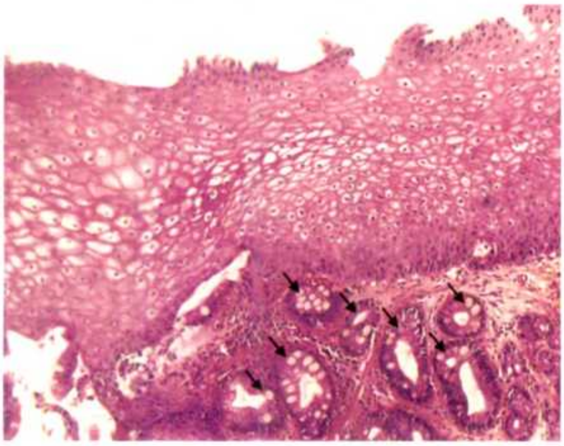
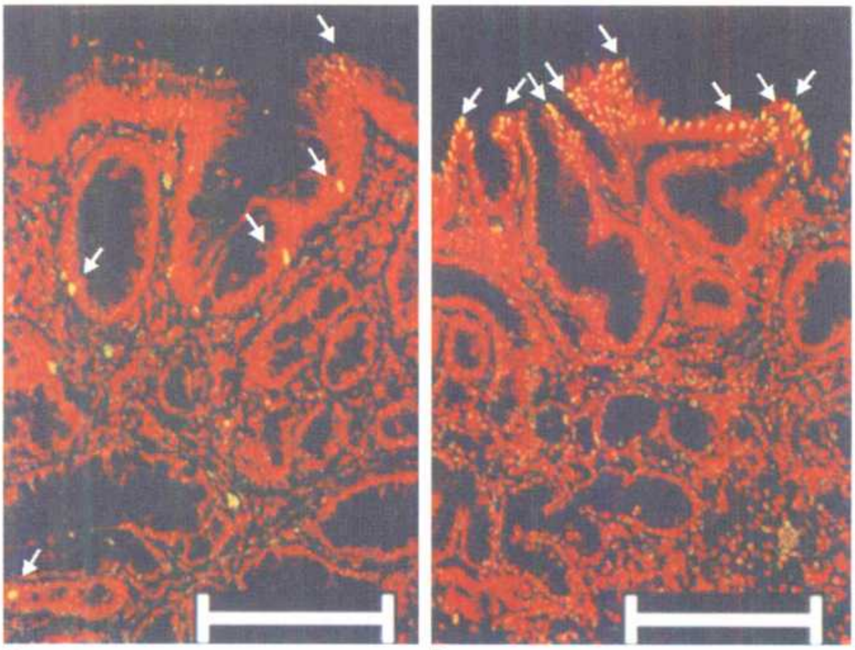


Fig. 1 Persistent intestinal metaplasia (arrows) after surgery can be seen beneath the squamous re-epithelialization (haematoxylin-phloxine-saffron stain, original magnification × 200)

Results

Endoscopy and biopsies

The 19 patients had 57 endoscopic examinations with multiple biopsies and documented intestinal metaplasia. They were chosen for the TUNEL immunohistochemistry study. Well oriented columnar-lined metaplasia crypts containing intestinal metaplastic cells were found in all sections at the low-magnification view and were used to calculate the apoptosis index. No regression of Barrett's epithelium (e.g. complete removal of intestinal metaplasia from the oesophagus) was observed in this patient series. Even for patients with postoperative squamous re-epithelialization ($n = 5$), intestinal metaplastic cells could still be found underneath (*Fig. 1*). A median of 1945 (range 1155–3650) epithelial cells per high-power field per section was counted to determine the apoptosis index in intestinal



a Intestinal metaplasia

b Gastric metaplasia

Fig. 2 Apoptosis in Barrett's mucosa. **a** In intestinal metaplasia a few apoptotic nuclei (bright yellow spots) can be seen both at the surface and in deep gland crypts (arrows). **b** In gastric metaplasia many apoptotic nuclei are found; they are usually located at the surface of the mucosa, as indicated by arrows. Bar, 0·2 mm

metaplasia zones. In 30 sets of biopsies only intestinal metaplasia was present. In the remaining 27 sets, both types of metaplasia were documented. Only the 27 sets of biopsies where both types of metaplasia were present were used to compare the different apoptosis indices in the two types of cell. This was completed for a median of 1757 (range 905–2450) gastric metaplastic epithelial cells per high-power field per section.

TUNEL immunohistochemistry

In the 27 biopsies that could be evaluated to calculate an apoptosis index for both intestinal and gastric metaplasia, intestinal metaplasia showed only a few apoptotic cells. In approximately one-third of specimens these apoptotic cells were also seen in deeper portions of the crypts (*Fig. 2a*). In gastric metaplasia many apoptotic cells were found, located mostly on the surface of the mucosa (*Fig. 2b*). The overall median apoptosis index in these two types of epithelium was 0·27 (i.q.r. 0·14–0·59) per cent for intestinal metaplasia and 2·14 (i.q.r. 1·03–3·20) per cent for gastric metaplasia ($P < 0{\cdot}001$, Wilcoxon signed ranks test).

Changes in the apoptosis index that occurred over the three observation periods (before operation, within 24 months and within 48 months after operation) are given in *Table 1*. The data were combined with previously published data[16] to derive a proliferation : apoptosis ratio. The results are given in *Fig. 3*.

In addition to postoperative endoscopy, oesophageal manometry and oesophageal 24-h pH monitoring were carried out. In four patients in whom 24-h pH monitoring demonstrated abnormal oesophageal acid exposure (more than 4 per cent of recording time with a pH of less than 4), the median apoptosis index was 0·41 (i.q.r. 0·20–0·46) per cent, compared with 0·59 (0·26–0·60) per cent in 15 patients who had no postoperative acid exposure ($P = 0{\cdot}91$, Mann–Whitney U test).

Table 1 Apoptosis index in Barrett's mucosa before and after antireflux surgery

	Apoptosis index (%)	
	Intestinal metaplasia ($n = 19$)	Gastric metaplasia ($n = 8$)
Before operation	0·23 (0·15–0·27)	2·16 (1·87–2·58)
After operation (months)		
0–23	0·42 (0·13–0·59)*	3·20 (2·96–4·56)*
24–46	0·59 (0·27–0·75)*	1·03 (0·89–1·50)*†
P	0·015‡	0·002§

Values are median (interquartile range). $^*P < 0{\cdot}05$ *versus* before operation; $^†P < 0{\cdot}05$ *versus* 0–23 months after operation (Student's t test). ‡Friedman test; §two-way analysis of variance

Discussion

Apoptosis removes genetically altered cells, thereby protecting tissue from neoplastic transformation. The balance between proliferation and apoptosis must be strictly regulated to sustain tissue homeostasis. An imbalance between the two processes can result in either unwanted tissue depletion or abnormal cell growth[13]. The intestinal phenotype of Barrett's oesophagus represents an unstable epithelium that is at risk of becoming dysplastic. This progression is associated with enhanced proliferation with a relatively low apoptotic activity[18,19].

The results of the present study indicate that although intestinal-type mucosa displays a higher proliferation state[16,20,21] it has significantly lower apoptosis index than gastric metaplasia. Thus the resultant higher proliferation : apoptosis ratio provides further evidence for the potential risk of malignant progression. The different distribution pattern of apoptotic cells between intestinal and gastric metaplasia may also reflect their different behaviour. Whittles *et al.*[19] found a greatly increased glandular proliferation : apoptosis ratio in the progression of metaplasia to dysplasia and adenocarcinoma. The reduced apoptosis seen in Barrett's oesophagus is considered to be responsible for this increasing proliferation : apoptosis ratio[22–24]. In parallel to these observations other authors have, however, reported increased apoptosis in intestinal metaplasia and dysplasia[18,19].

The different gene expression levels in Barrett's mucosa also indicate the malignant potential of the intestinal phenotype in Barrett's oesophagus. Younes *et al.*[25] found

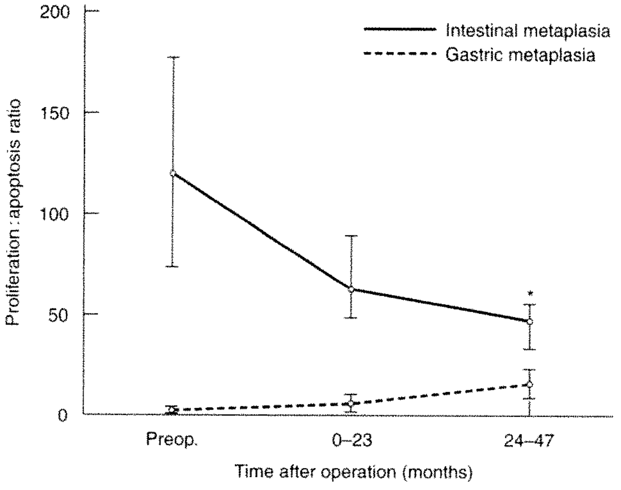


Fig. 3 Proliferation : apoptosis ratio in Barrett's oesophagus before and after antireflux surgery. Values are median (interquartile range). $^*P < 0{\cdot}001$ (two-way analysis of variance)

that Fas was detected less frequently in intestinal metaplasia. Moreover, Campomenosi *et al.*[26] showed that the *p53* mutation was more frequently observed in intestinal metaplasia than in non-intestinal metaplastic mucosa. These observations, in addition to those of the present study, may explain why intestinal metaplasia is the most closely associated event during the development of adenocarcinoma.

The effects of antireflux surgery on apoptosis in Barrett's oesophagus have not been investigated thoroughly. Wetscher *et al.*[24] studied apoptosis in the oesophageal biopsies of 39 patients with reflux oesophagitis, including 18 with Barrett's oesophagus undergoing laparoscopic antireflux surgery. With 6 months' endoscopic follow-up, they found that apoptosis increased with the severity of oesophagitis but remained low in Barrett's oesophagus without differentiating gastric and intestinal metaplastic cells. This low rate of apoptosis did not change after operation. Their results are similar to the findings with gastric metaplasia reported here. There was a slight increase in apoptosis immediately after operation followed by a decrease, in parallel with a decrease in proliferative activity. In intestinal metaplasia the present results show a continuous increase in apoptosis after antireflux surgery, whereas proliferation decreases later on. Thus the proliferation : apoptosis ratio decreased in intestinal metaplasia while it remained relatively stable and low in gastric metaplasia both before and after operation. The increase of proliferation and apoptosis in both intestinal and gastric metaplasia reflects a tissue response of the oesophageal epithelium secondary to operative trauma. Over a longer observation time of 2–4 years the rate of apoptosis in intestinal metaplasia increased significantly. The authors believe that antireflux surgery may provide long-lasting protection against progression toward dysplasia in Barrett's mucosa. This has been further substantiated clinically by Katz *et al.*[27] and McCallum *et al.*[28], who observed a much lower incidence of dysplasia or adenocarcinoma in patients with Barrett's oesophagus who had an antireflux operation than in patients treated with medication alone.

Even after antireflux surgery, abnormal oesophageal acid exposure may be recorded in some patients with gastro-oesophageal reflux and/or Barrett's oesophagus[17,29]. It is well documented that acid exposure can induce cellular hyperproliferation both in Barrett's mucosa and in normal oesophageal submucosal glands[30,31]. However, to date, the effects of acid exposure on apoptosis have not been documented extensively. Apoptosis increases in oesophagitis in parallel with an increase in cell proliferation. In Barrett's oesophagus, apoptosis is inhibited and the rate becomes even lower in severe oesophagitis[19,24]. Souza *et al.*[32] recently observed that exposure of Barrett's oesophagus to acid can activate the mitogen-activated protein (MAP) kinase pathway and alter the proliferation : apoptosis ratio in the human Barrett's-associated oesophageal carcinoma cell line. They found that one of MAP kinases, p38, is activated after 3 min of acid exposure. This mediates and accelerates the process of cell growth and decreases apoptosis. These authors concluded that episodes of acid reflux might predispose to cancer progression by triggering both a pro-proliferative and an antiapoptotic signal pathway in the oesophagus of patients with Barrett's oesophagus and adenocarcinoma. The present study has shown that patients with persistent postoperative acid exposure have a lower apoptosis index, while previous observations have indicated an increased proliferation in intestinal metaplasia[16]. Although the numbers are fewer, the observation suggests a potential risk for malignant progression in this subgroup of patients.

In summary, in Barrett's oesophagus the intestinal metaplastic cells show reduced apoptosis that is not seen in gastric metaplastic cells. This suggests that intestinal metaplasia is the histological cell type that predisposes to malignant transformation. Immediately after antireflux surgery there is an increase in apoptosis in parallel with the increase of proliferation. This may be an adaptation mechanism of the oesophageal columnar mucosa following surgical manipulation. Over time, a steady increase in apoptosis and a decrease in proliferation of intestinal metaplasia occur. Thus, correction of acid reflux may provide the Barrett's mucosa with protection against the development of dysplasia or carcinoma. Persistent postoperative acid exposure may increase the risk of malignancy.

Acknowledgements

This work was supported by the Research and Development Fund, Society of Montreal Thoracic Surgeons, University of Montreal Medical Centre, Montreal, Canada.

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Original article

Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer

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Background: Patients who undergo major surgery for cancer are at high risk of postoperative infection. Postoperative immunosuppression may be due to dysregulation of cytokine production. The aim of this study was to investigate the association between changes in serum proinflammatory and anti-inflammatory cytokine concentrations and postoperative septic complications after major surgery.

Methods: Serial blood samples were collected from 30 consecutive patients for determination of serum cytokine levels. Healthy volunteers were used as the control group.

Results: Eleven patients developed no complications (group 1), 14 developed sepsis or severe sepsis (group 2), and five developed septic shock (group 3). On day 1 the patients in groups 2 and 3 had significantly higher levels of interleukin (IL) 6 than those in group 1. IL-6 levels remained high until day 5. Tumour necrosis factor (TNF), IL-1, interferon (IFN) γ and IL-12 levels were not affected by surgical trauma or by the occurrence of septic complications. After operation the circulating IL-1 receptor antagonist (IL-1ra) concentration was increased in all groups, but patients in group 3 had significantly higher levels of IL-1ra than those in group 1. IL-1ra levels correlated with IL-6 levels. The pattern of IL-10 levels was similar to that of IL-1ra levels.

Conclusion: Serum concentrations of proinflammatory cytokines (TNF, IL-1, IFN-γ and IL-12) were not affected by operation or the occurrence of septic complications. The postoperative increase in IL-6 concentration was associated with septic morbidity, while raised IL-1ra concentration was associated with postoperative septic shock.

Paper accepted 13 June 2002

British Journal of Surgery 2002, 89, 1450–1456

Introduction

Patients undergoing major oncological resection are at high risk of postoperative infectious complications[1]. Recent therapeutic advances, both medical and surgical, have enabled clinicians to reduce early postoperative mortality rates. Despite this progress, certain patients remain at high risk of infection and the attendant risk of increased morbidity and mortality. The immunosuppression that occurs after severe accidental or surgical trauma contributes to this predisposition[2]. Postsurgical immunosuppression may be due to a direct effect of anaesthetic drugs on immune response, hormonal changes evoked by stress, the effect of haemorrhage and transfusion, or the extent of surgical trauma[3–7]. It may also be due to the dysregulation of cytokine production. Hence, plasma levels of interleukin (IL) 6 are increased after surgical trauma and are associated with the duration of anaesthesia and operation, the extent of surgical trauma, immune dysfunction, postoperative systemic inflammatory response syndrome (SIRS) and outcome after operation[8]. Moreover, it is controversial whether the circulating level of proinflammatory cytokines (IL-1β and tumour necrosis factor (TNF)) or cytokines involved in an efficient cell-mediated immune response (IL-12 and interferon (IFN) γ) are involved in the postoperative inflammatory response[9,10]. In addition, the activity of circulating inflammatory cytokines may be modulated by anti-inflammatory cytokines[11]. Thus postoperative immunosuppression could be linked to the production of

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

anti-inflammatory cytokines such as IL-10[12] and IL-1 receptor antagonist (IL-1ra)[13]. Surgical patients may also develop immunosuppression if the balance between pro-inflammatory and anti-inflammatory mediators is lost. This immunosuppression is described as the compensatory anti-inflammatory response syndrome[14] (CARS) and may be of importance in the pathophysiology of sepsis and organ failure after major injury. As IL-6 may act as a pro-inflammatory or an anti-inflammatory cytokine[15,16], its biological role in the adverse effects of surgical trauma remains to be clarified.

The aim of this study was to investigate the association between changes in serum proinflammatory and anti-inflammatory cytokine concentrations and postoperative septic complications after major cancer surgery.

Patients and methods

The study was conducted prospectively over a period of 10 months in a cancer hospital. After obtaining the informed consent of patients and approval from the hospital's ethics committee, the study was conducted on 30 consecutive patients undergoing elective major surgical procedures. The criteria for inclusion were major tumour resection (digestive tract or gynaecological cancers) and expected duration of operation of 5 h or more. The preoperative factors for non-inclusion were age less than 18 years, emergency operation, preoperative treatment with anti-inflammatory drugs, the existence of a preoperative infection or clinical inflammatory syndrome, treatment with corticosteroids or morphine, and immunosuppressive illness other than the neoplasm for which the patient was being treated.

All patients received a standardized premedication and anaesthesia protocol. Premedication (the night before and on the morning of operation) consisted of hydroxyzine (100 mg orally). Induction of anaesthesia was performed with propofol (3 mg/kg) and fentanyl (3 μg/kg). Muscle relaxation was achieved with atracurium at a dose of 0·5 mg/kg for intubation. Anaesthesia was maintained with an inhaled halogen agent (isoflurane 1–1·5 minimum alveolar concentration) in a mixture of 50 per cent oxygen and 50 per cent nitrous oxide, together with repeated injections of fentanyl. Muscle relaxation was maintained by repeated injection of atracurium as required. Antibiotic prophylaxis consisted of amoxicillin 2 g and clavulanic acid 200 mg, with half that dose repeated every 2 h. All patients were given protection against peroperative hypothermia (intravenous fluids were administered through a fluid warmer; a forced-air cover was positioned over the upper or lower body set to deliver air at 40°C).

All clinical and paraclinical data were collected prospectively for each patient. The Charlson co-morbidity index was originally designed to quantify underlying diseases and to classify prognostic co-morbidity[17]. Patients were distributed into three groups according to the occurrence of septic complications during the postoperative period: uncomplicated (group 1), sepsis or severe sepsis (group 2), and septic shock (group 3). Sepsis was defined as SIRS associated with infection according to Bone's criteria[18]. Signs of sepsis were: body temperature less than 35·6°C or more than 38·3°C; tachycardia (more than 90 beats per min); respiratory rate greater than 20 breaths per min or an arterial partial pressure of carbon dioxide lower than 32 mmHg (unless the patient was mechanically ventilated); a white cell count of 12×10^9 per litre or more, or of 4×10^9 per litre or less; or more than 10 per cent immature neutrophils (bands). Severe sepsis was defined as: sepsis with evidence of organ dysfunction and hypoperfusion; acute alteration of mental status; raised plasma lactate concentration; unexplained metabolic acidosis (arterial pH less than 7·3); hypoxaemia (arterial partial pressure of oxygen ($P\text{aO}_2$) lower than 70 mmHg when breathing room air, or an acute drop in $P\text{aO}_2$ of more than 15 mmHg below baseline when breathing room air, or hypoxaemia requiring mechanical ventilation); prolonged prothrombin time or a decrease in the platelet count of more than 50 per cent or to 100×10^9 per litre or less; oliguria; and hypotension, defined as systolic blood pressure lower than 90 mmHg or a decrease of more than 40 mmHg from the baseline. Septic shock was defined as hypotension in addition to sepsis syndrome persisting despite adequate fluid resuscitation and requiring inotropic support.

Standard supportive care, surgical procedures (e.g. drainage of abscesses) and administration of broad-spectrum antibiotics were provided to all patients with sepsis. Pneumonia was diagnosed if infiltrations were present on the chest radiograph and, if possible, a positive culture from purulent sputum or bronchial fluid was obtained. Abscesses and peritonitis were diagnosed by ultrasonography or computed tomography, together with growth of pathogenic bacteria from aspirated pus. Urinary tract infections were diagnosed by evidence of leucocyturia, haematuria and growth of a pathogen in urine culture. Septic complications were recorded until the tenth postoperative day. All other clinical data were recorded during the patient's stay in the intensive care unit (ICU).

Blood sampling

Blood samples were collected in glass tubes before operation and on the first, second, third and fifth mornings after operation. The samples were processed within 2 h and the sera were stored at − 20°C. Cytokine measurement was performed after the clinical data had been recorded. A group of 14 healthy adults were used as controls for the preoperative values.

Cytokine determination

Levels of circulating cytokines were measured in duplicate by enzyme immunoassay. IL-6, IL-10 and TNF were determined using kits provided by Immunotech (Marseilles, France). The minimum detectable concentrations were 3, 5 and 5 pg/ml respectively. IL-1ra was assayed using a kit provided by R&D Systems (Abingdon, UK) with a sensitivity of 22 pg/ml. The intra-assay and interassay coefficients of variation of the immunoassay kits ranged between 5 and 10 per cent.

Statistical analysis

Values concerning the clinical characteristics of patients are expressed as mean(s.e.m.). Cytokine concentrations are also presented as mean(s.e.m.), and these parameters were compared with those obtained on day 0 in the control group, using the Mann–Whitney *U* test. For two independent groups, the Mann–Whitney *U* test was performed. Variables found to be significant at the level of $P < 0{\cdot}05$ were considered eligible for multivariate analysis. A logistic regression analysis was used to determine independent factors associated with all postoperative septic complications. For intragroup changes, the Friedmann multiple comparison test was performed. To investigate the correlation between two single variables, Spearman correlation was performed. $P < 0{\cdot}05$ was considered significant.

Results

Thirty consecutive patients were included in the study (pelvic exenteration, 13; peritonectomy, six; oesophagectomy, eight; gastrectomy, three). Eleven patients had no postoperative complication (group 1), 14 developed sepsis or severe sepsis (group 2), and five developed septic shock (group 3). The perioperative clinical profiles of each group are shown in *Table 1*.

Table 1 Clinical characteristics of the three groups of patients

	Uncomplicated (n = 11)	Sepsis or severe sepsis (n = 14)	Septic shock (n = 5)
Age (years)	57·7(4·0)	58·5(2·0)	48·8(4·0)
Sex ratio (M : F)	5 : 6	8 : 6	3 : 2
Charlson co-morbidity index*	3·5(0·6)	5·0(0·8)	8·6(0·4)‡
APACHE II score on day 1†	6·4(0·7)	8·7(0·7)‡	10·8(2·0)‡

Values are mean(s.e.m.). *Quantifies underlying diseases[17]. †Acute Physiology And Chronic Health Evaluation II score[19]. ‡$P < 0{\cdot}05$ *versus* uncomplicated group (Mann–Whitney *U* test)

Table 2 Preoperative cytokine levels in study patients and controls

	Study patients (n = 30)	Controls (n = 14)
IL-6 (pg/ml)	22·2(6·4)*	3(0)
IL-1 receptor antagonist (pg/ml)	783(196)	661(190)
IL-10 (pg/ml)	5·3(0·4)	7·1(2·1)
Tumour necrosis factor α (pg/ml)	25·6(10·5)*	5·5(0·4)

Values are mean(s.e.m.). IL, interleukin. *$P < 0{\cdot}05$ *versus* control (Mann–Whitney *U* test)

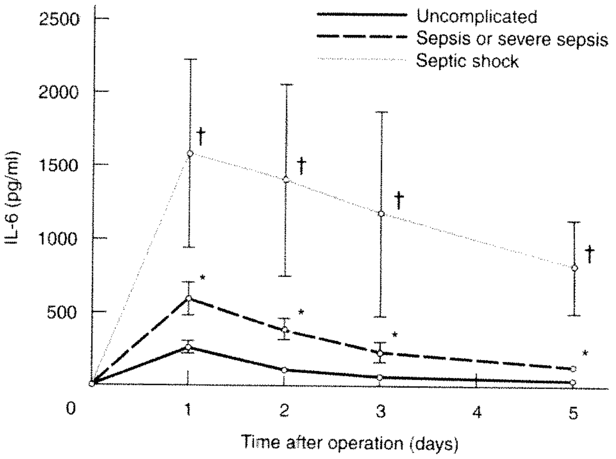

Fig. 1 Interleukin (IL) 6 levels for the three patient groups. Values are mean(s.e.m.). *$P < 0{\cdot}01$, †$P < 0{\cdot}003$ *versus* uncomplicated group (Mann–Whitney *U* test)

Interleukin 6 level

On day 0, IL-6 levels were significantly higher ($P < 0{\cdot}001$) in patients compared with healthy controls (*Table 2*) and there were no differences between the three patient groups (*Fig. 1*). After operation, circulating levels of IL-6 increased significantly in all three groups compared with values obtained on day 0 ($P < 0{\cdot}001$, $P < 0{\cdot}001$ and $P < 0{\cdot}003$ respectively, Friedmann test). However, the increase was significantly greater in groups 2 and 3 than in group 1 on all days ($P < 0{\cdot}01$ and $P < 0{\cdot}003$ respectively) (*Fig. 1*). For patients, a significant correlation was found between IL-6

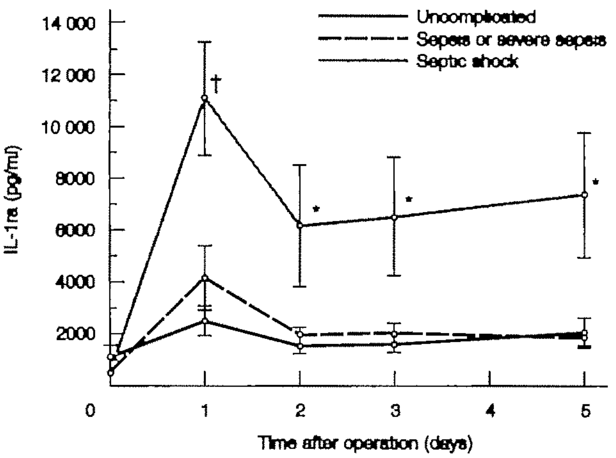

Fig. 2 Interleukin 1 receptor antagonist (IL-1ra) levels for the three patient groups. Values are mean(s.e.m.). $^*P < 0{\cdot}04$, $^\dagger P < 0{\cdot}004$ *versus* uncomplicated group (Mann–Whitney *U* test)

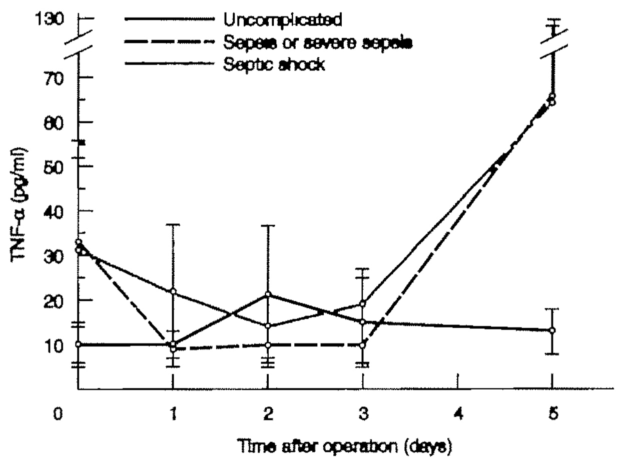

Fig. 4 Tumour necrosis factor (TNF) α levels for the three patient groups. Values are mean(s.e.m.)

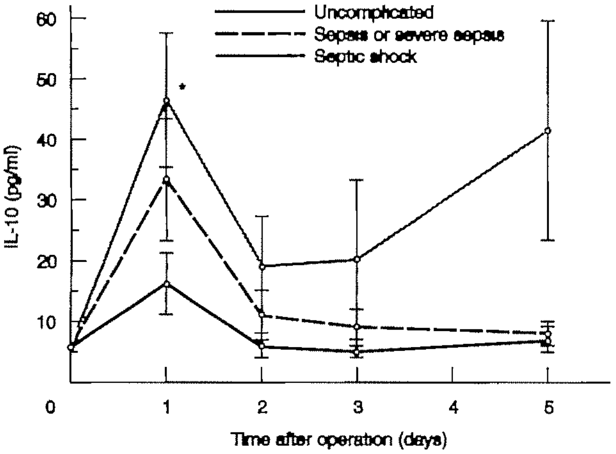

Fig. 3 Interleukin (IL) 10 levels for the three patient groups. Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* uncomplicated group (Mann–Whitney *U* test)

concentrations on day 1 and the Charlson co-morbidity index ($r^2 = 0{\cdot}16$, $P = 0{\cdot}02$), length of operation ($r^2 = 0{\cdot}77$, $P = 0{\cdot}04$) and duration of mechanical ventilation in the ICU ($r^2 = 0{\cdot}76$, $P = 0{\cdot}001$). In addition, IL-6 levels returned progressively to normal values between day 1 and day 5 in group 1 patients, whereas they remained high in patients in groups 2 and 3 (*Fig. 1*).

Interleukin 1 receptor antagonist

The circulating levels of IL-1ra were similar in healthy controls and patients before operation (*Table 2*) and there were no significant differences between the three patient groups (*Fig. 2*). After operation, circulating levels of IL-1ra increased significantly in all three groups compared with values on day 0 ($P < 0{\cdot}04$, $P < 0{\cdot}001$ and $P < 0{\cdot}004$ respectively, Friedmann test). IL-1ra levels were greatly increased in group 3 patients, compared with those in group 1 (*Fig. 2*). For patients, a significant correlation existed between IL-1ra levels on day 1 and duration of anaesthesia ($r^2 = 0{\cdot}24$, $P = 0{\cdot}03$) and length of stay in the ICU ($r^2 = 0{\cdot}39$, $P = 0{\cdot}007$). Thereafter, IL-1ra levels returned to normal in group 1. In contrast, IL-1ra levels remained higher in group 3 compared with those in group 1. For patients, IL-1ra and IL-6 levels were correlated on day 1 ($r^2 = 0{\cdot}23$, $P = 0{\cdot}001$), day 2 ($r^2 = 0{\cdot}77$, $P = 0{\cdot}02$), day 3 ($r^2 = 0{\cdot}57$, $P < 0{\cdot}001$) and day 5 ($r^2 = 0{\cdot}63$, $P = 0{\cdot}006$).

Interleukin 10 levels

IL-10 levels were similar in healthy controls and patients before operation (*Table 2*). After operation circulating levels of IL-10 increased significantly in all three patient groups ($P < 0{\cdot}05$, $P < 0{\cdot}001$, $P < 0{\cdot}05$ respectively, Friedmann test); on day 1 levels were significantly increased in group 3 compared with group 1 (*Fig. 3*).

Tumour necrosis factor levels

The TNF values on day 0 were slightly but significantly higher in study patients compared with healthy controls (*Table 2*), but no differences were observed between the three patient groups (*Fig. 4*). Circulating levels of TNF did not vary during the postoperative period in the three patient groups (*Fig. 4*).

Other measurements

Circulating levels of IL-1β, IL-12 and IFN-γ were measured in patients and controls. On day 0 and during the postoperative period, these cytokines remained undetectable (data not shown).

On logistic regression analysis of the Charlson comorbidity index, Acute Physiology And Chronic Health Evaluation (APACHE) II scores, IL-1ra (day 1) and IL-6 (day 1), only IL-6 (day 1) was an independent predictor of postoperative septic complications ($P = 0.02$).

Discussion

Circulating levels of cytokines induced by major cancer surgery were studied in order to evaluate their association with the occurrence of postoperative infectious complications. The study confirms the importance of septic complications in this situation[1]. After operation IL-6 levels in group 1 were increased in comparison with day 0 but normalized with time, suggesting that surgical trauma induced the immediate and temporary postoperative increase in IL-6 concentration. However, on day 1 patients in groups 2 and 3 had IL-6 levels that were, respectively, two and six times higher than those in group 1 patients. In addition, they remained high during the course of the study. These high levels of IL-6 were independently associated with postoperative septic events and correlated with postoperative morbidity (length of ICU stay and duration of mechanical ventilation) in accordance with the findings of other studies[20,21]. As septic events always occurred after day 2 in the present study, IL-6 is probably an early indicator of postoperative infection following the trauma of major oncological surgery.

As IL-6 is known to act partly as an inflammatory cytokine, circulating levels of other known inflammatory cytokines were also studied. On day 0 the circulating levels of TNF were higher in patients than in controls, but were still at the relatively low levels observed in patients with a variety of solid cancers[22]. TNF concentration did not vary in the immediate postoperative period. The lack of variation in TNF concentration after surgical or other severe trauma has also been noted by others[20,21,23]. IL-1β remained undetectable. According to Baigrie *et al.*[21], IL-1β secretion occurs 3 h after major surgery and returns to normal soon afterwards. However, in the present study patients were sampled daily, suggesting that the interval during which detectable IL-1β could have been present might have been missed. The cytokines involved in the immune cell response (IL-12 and IFN-γ) remained undetectable. The circulating levels of cytokines such as TNF, IL-1β, IL-12 and IFN-γ did not seem to be related to increased levels of IL-6.

As IL-6 could act as an immunoregulatory cytokine, IL-1ra and IL-10 were also studied. IL-1ra concentration increased in all study patients during the postoperative period. Anaesthetic technique probably influences the postoperative secretion of IL-1ra[13]. Postoperative levels of IL-1ra were correlated with the duration of anaesthesia on day 1. After operation the IL-1ra level was significantly higher in group 3 than in group 1, and these levels were found to correlate with those of IL-6. These results are in agreement with previous reports[16,24].

The significant rise in IL-1ra secretion that preceded postoperative septic shock suggests a role for IL-1ra in the aetiology of this complication. This hypothesis is supported by the observation of a moderate postoperative increase in IL-10 concentration in the three groups of patients, which was expected because surgical trauma is known to induce the secretion of IL-10[12,13]. However, patients who went on to develop septic shock demonstrated an increase in IL-10 concentration that was significantly higher than that in patients who did not. Thus circulating IL-10 could be involved in the immunosuppression that is associated with major abdominal surgery and postoperative septic complications[12,25,26].

The predominance of postoperative anti-inflammatory response, as suggested by several reports, favours postoperative immunosuppression[2,5,12,14]. As cytokine secretion can be altered by co-morbidity factors[27,28], such postoperative immunosuppression may be influenced by patients' preoperative status. In fact, the Charlson comorbidity index correlated significantly with the postoperative serum concentration of IL-6. In addition patients who developed septic shock in the postoperative period had the highest Charlson co-morbidity index before operation. This suggests that postoperative SIRS and sepsis are favoured by the preoperative clinical–biological status of patients[14]. In the present study patients did not develop any biological postoperative inflammatory response (low TNF-α, IL-1, IL-12 and IFN-γ serum concentrations), but in contrast developed a marked anti-inflammatory response (high IL-10 and IL-1ra serum levels). This situation represents a genuine postoperative CARS in reaction to the initial surgical trauma[14]. IL-6 could play an important role in postoperative CARS by promoting the release of IL-1ra, because levels of both cytokines were correlated, as reported in other studies[16,24]. Their secretion could be responsible for the absence of IL-12 and IFN-γ secretion[25,29,30] and therefore result in an altered postoperative antibacterial immune response[10,29]. Furthermore, IL-6 and

IL-1ra could be early markers of septic shock, as has already been demonstrated in certain forms of sepsis[31].

In conclusion, patients who undergo major cancer surgery are at high risk of postoperative infection. During the early postoperative period, IL-6 could play a pivotal role given its participation in postoperative SIRS and the fact that it correlated with anti-inflammatory cytokines (IL-1ra and IL-10). The magnitude of postoperative CARS could explain why only some patients, and not others, develop postoperative sepsis. Anti-inflammatory cytokines may be early markers of postoperative septic shock.

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Original article

Granulocyte colony-stimulating factor but not peritoneal lavage increases survival rate after experimental abdominal contamination and infection

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Background: The value of peritoneal lavage for intra-abdominal contamination and infection has never been proven scientifically. In contrast, the stimulation of host defence mechanisms with cytokines such as granulocyte colony-stimulating factor (G-CSF) has appeared promising in recent clinical trials.

Methods: Clinic modelling randomized trials (CMRTs), which model the complexity of the clinical reality, were used in rats in which peritoneal contamination and infection (PCI) was produced with human stool bacteria. The following groups were compared: trial 1, intraoperative peritoneal lavage with saline *versus* taurolin (18 rats per group); trial 2, no lavage *versus* saline lavage *versus* saline lavage plus subcutaneous administration of G-CSF (18 rats per group); trial 3, lavage with saline *versus* no lavage (30 rats per group). The primary endpoint was mortality at 120 h. Secondary endpoints were the phagocytic activity of granulocytes, and systemic and peritoneal cytokine levels.

Results: In trial 1 lavage with taurolin was not superior to that with saline (five of 18 *versus* eight of 18 animals survived; $P = 0{\cdot}32$). In trial 2, six of 18 animals having no lavage and three of 18 receiving saline lavage survived. The combination of lavage and G-CSF increased the number of animals surviving to 11 of 18 ($P < 0{\cdot}05$). Lavage combined with G-CSF stimulated granulocyte phagocytic activity ($P < 0{\cdot}01$) and reduced the levels of interleukin (IL) 6 ($P < 0{\cdot}01$) and tumour necrosis factor α ($P < 0{\cdot}05$) in peritoneal fluid, as well as plasma levels of IL-6 ($P < 0{\cdot}05$) and IL-10 ($P < 0{\cdot}01$). In trial 3, survival was not significantly different in animals having lavage (14 of 30) and no lavage (19 of 30) ($P = 0{\cdot}14$).

Conclusion: In these CMRTs of intra-abdominal contamination and infection, peritoneal lavage was not beneficial, but when lavage was combined with subcutaneous administration of G-CSF mortality was reduced and the local and systemic cytokine response was downgraded. Results from these CMRTs were used directly to define the trial conditions of a randomized clinical trial with G-CSF. Peritoneal lavage is not recommended.

Paper accepted 12 June 2002

British Journal of Surgery 2002, **89**, 1457–1464

Introduction

Even in today's era of evidence-based medicine, the management of intra-abdominal infection is influenced more by local dogma than by the evidence. The only widely accepted strategies are the necessity to perform source control and to administer systemic antibiotics. In order to reduce treatment heterogeneity in a randomized controlled trial, an evidence-based guideline for the management of anastomotic leakage was developed[1]. Comparing saline lavage with no lavage, the only randomized clinical trial available demonstrated no benefit[2]. Better results were promised by the use of bacteriostatic agents[3] (e.g. taurolin, povidone–iodine) or antibiotics[4,5] (e.g. metronidazole, tetracycline) in the lavage solution. However, two collective reviews of the literature[6,7] concluded that there is no evidence that lavage of the contaminated and infected peritoneal cavity, with or without additives to the lavage solution, is advantageous. In most institutions, specific strategies based on local experience are used to decide whether or not abdominal lavage is performed[8].

In contrast to lavage, the administration of immunoregulatory agents such as granulocyte colony-stimulating factor (G-CSF) was commenced in clinical use only after clinical trials had demonstrated their effectiveness. Today, G-CSF is used most often in patients with cancer who are receiving high-dose chemotherapy[9] and for stem cell mobilization and harvesting[10]. In infectious disease G-CSF stimulates the host defence[11–13] and reduces the proinflammatory cytokine response[14,15]. In certain types of infection, such as diabetic foot[16] and neutropenic pneumonia[17], the clinical effectiveness of G-CSF has been proven, but this is not the case for intra-abdominal infection.

The aim of this study was to reproduce the complexity of the clinical situation in clinic modelling randomized trials (CMRTs), in order to analyse the effects of intraoperative lavage, different lavage solutions (saline and taurolin) and the addition of G-CSF prophylaxis. The findings were implemented together with the evidence from the literature in the guidelines for management of postoperative anastomotic leakage in the ongoing clinical G-CSF trial[1].

Materials and methods

The concept of clinic modelling randomized trials

In line with the CONSORT statement[18] for clinical trials, the CMRT concept for animal trials was developed[19]. No model can contain all the elements and complexities from the actual clinical situation: models always simplify or add to the real situation[20]. The purpose of CMRTs is to help in the design of clinical trials[21]. In this study, a rat faecal peritonitis model[22] was chosen to model the conditions of clinical trials (sample size calculation, randomization, double-blinding, clinically relevant endpoint, search for positive and negative results, 'intent to treat rule', documentation of withdrawals, adequate statistical analysis) and clinical complexity (mortality rate of about 50 per cent, anaesthesia (fentanyl–droperidol), preoperative antibiotic prophylaxis, volume substitution, supportive interventions (G-CSF), operation, contamination with stool bacteria, analgesia).

Course of the experiments

Some 12 h before operation rats were weighed and food (standard diet; Altromin, Lage, Germany) was withheld. Animals in trial 2 were injected subcutaneously with G-CSF 20 μg/kg body-weight (filgrastim; Amgen, Munich, Germany) three times: 12 h before, and 12 and 36 h after, peritoneal contamination and infection (PCI). This time schedule had been shown to be the most effective in previous CMRTs[19] and was, for this reason, also used in an ongoing clinical trial[23]. The rats in the control groups were treated with Ringer solution. Anaesthesia was induced with a combination of fentanyl and droperidol (0·2 and 10 mg/kg respectively) intraperitoneally 1 h before operation. After tail vein cannulation 2 ml Ringer solution was administered, and 1 h before operation antibiotic prophylaxis (co-amoxiclav 10 mg/kg; SmithKline Beecham, Munich, Germany) was given. For PCI, laparotomy was performed through a midline incision 2 cm in length. A standardized stool inoculum[22], in a volume of 1·2 ml/kg diluted 1 : 5 in Ringer solution, was injected into the pelvic region. The wound was closed in two layers with 2/0 silk using an interrupted technique. Postoperative analgesia was with tramadol (Mundipharm, Limburg, Germany) 20 mg/kg daily, administered subcutaneously. After operation the animals received food and water *ad libitum*. All rats that survived for 24 h after PCI were anaesthetized again and received antibiotic prophylaxis as before. At the end of the trials (after 120 h) survivors were killed by carbon dioxide intoxication. Autopsy was performed to localize adhesions, pus and other pathological changes.

Permission for the animal experiments was given by the regional animal welfare committee (Giessen, Germany).

Trial 1: different lavage solutions (taurolin *versus* saline)

The study population consisted of male Wistar rats weighing 200–250 g, obtained from Charles River Wiga, Sulzfeld, Germany. Rats were allocated to two groups (18 animals per group): animals in group 1 received PCI plus antibiotics plus saline lavage; those in group 2 had PCI plus antibiotics plus taurolin lavage.

Randomization to the two groups was performed by simple random permutation. Blinding was carried out at the time of laparotomy and lavage. The primary endpoint was survival at 120 h. The sample size of 36 rats was calculated using the formula of Friedman *et al.*[24], estimating a 50 per cent change ($\delta = 0{\cdot}5$) between control and treatment groups with an α error of 0·025 and a power of $1 - \beta = 0{\cdot}9$.

Some 24 h after PCI the silk sutures were removed, the abdomen was reopened and intra-abdominal debridement of faeces and pus was performed with sterile wet gauze. For peritoneal lavage, prewarmed (37°C) isotonic saline solution (2 × 20 ml) was used to wash all parts of the abdominal cavity. The lavage solution (20 ml saline or 0·5 per cent taurolin–Ringer solution (Hoechst, Frankfurt, Germany)) was left in the abdominal cavity at the second lavage for 1 h to obtain an optimal response to taurolin. Afterwards the solution was withdrawn by suction with a catheter on a syringe and the wound was closed again using silk.

Trial 2: prophylaxis with granulocyte colony-stimulating factor and lavage with saline

Previous trials have shown that G-CSF increases the survival rate, but the interaction with abdominal lavage has not been studied. As well as determining survival at 120 h, bacterial phagocytosis of granulocytes and cytokine levels in peritoneal fluid and plasma were measured before and after lavage. The control group did not undergo relaparotomy. Rats were allocated to three groups (18 animals per group): animals in group 1 had no relaparotomy and no lavage (PCI plus antibiotics only); animals in group 2 had PCI plus antibiotics plus saline lavage; animals in group 3 had PCI plus antibiotics plus saline lavage plus G-CSF prophylaxis.

Trial 3: abdominal lavage with saline

Based on the results of trial 2, another sample-size calculation was performed with $\alpha = 0{\cdot}05$; $1 - \beta = 0{\cdot}8$; $p_1 = 0{\cdot}1$; $p_2 = 0{\cdot}4$; $\delta = 0{\cdot}3$ to analyse the influence of lavage on the survival rate in a trial with 30 rats per group. The abdomen of animals in both groups was reopened and debridement was carried out. Animals in group 1 had no lavage (PCI plus antibiotics plus mechanical cleansing of the abdominal cavity); those in group 2 also had lavage (PCI plus antibiotics plus mechanical cleansing plus saline lavage).

Phagocytosis and cytokines

Blood was taken 1 and 24 h after PCI from the retro-orbital plexus randomly from nine rats in each group. Half of each group was not stressed by blood sampling. To measure phagocytosis, blood was supplemented with heparin (Liquemin®; Roche, Basle, Switzerland) 500 units/ml; for cytokine determination ethylenediamine tetra-acetic acid (EDTA) vials (Sarstedt, Nümbrecht, Germany) were used. At the same time, phagocytosis of *Escherichia coli* was determined by flow cytometry (FACScan®; Becton Dickinson, Oxford, UK) with the Phagotest® kit (Orpegen-Pharma, Heidelberg, Germany). For cytokine determination 1 ml peritoneal fluid was aspirated with a syringe before lavage (+ 24 h) and after lavage (+ 48 h). Determination of interleukin (IL) 6 and tumour necrosis factor (TNF) α levels in these samples was performed by means of enzyme-linked immunosorbent assay (ELISA) (rat ELISAs from Pharmingen, Heidelberg, Germany).

Statistical analysis

Survival analysis was performed with the log rank test. For analysis of equivalence the Pearson χ^2 test of independence with a test level of 0·05 was used. Ordinal data were analysed with Kruskal–Wallis analysis of variance. For multiple testing a Bonferroni correction was used. Ordinal data are given as mean(s.e.m.). $P < 0{\cdot}05$ was considered to be statistically significant.

Results

Trial 1: different lavage solutions (taurolin *versus* saline)

Before allocation, no rat died but three did not complete the trial (two in group 1 and one in group 2). These animals were withdrawn because they died before reoperation at 24 h from anaesthetic complications or sepsis (*Fig. 1*). Using the intention-to-treat rule, nine of 16 animals in the group receiving saline lavage survived, compared with five of 17 animals receiving taurolin lavage ($P = 0{\cdot}32$, log rank test).

Trial 2: prophylaxis with granulocyte colony-stimulating factor and lavage with saline

All rats completed the trial, with no technical, anaesthetic or other complications. Six of the 18 animals receiving saline lavage survived, compared with only three of 18 having no lavage (*Fig. 2*). Prophylaxis with G-CSF in combination with lavage doubled the proportion of animals surviving (11 of 18) ($P < 0{\cdot}05$, log rank test). No differences between the three groups were observed at autopsy.

The phagocytic activity of granulocytes treated *in vivo* with G-CSF was increased 1 h after PCI: the mean(s.e.m.) rate of phagocytosis was 40(8·7) per cent with G-CSF prophylaxis *versus* 31(11·2) per cent in animals receiving only lavage or no lavage ($P < 0{\cdot}05$, χ^2 test). At 24 and 48 h after PCI there was no difference in phagocytic activity between the groups.

Cytokine levels in plasma were markedly lower than in the peritoneal fluid at all sampling times (+ 24 h, + 48 h) (*Fig. 3*). Plasma levels of IL-6 (*Fig. 3a*) and IL-10 (*Fig. 3e*) were significantly reduced by G-CSF prophylaxis prior to lavage. No difference was seen in the TNF-α concentration before lavage (+ 24 h) and 24 h after lavage (+ 48 h) (*Fig. 3c*). Lavage had no influence on cytokine levels in either plasma or peritoneal fluid (24 h after lavage). In contrast G-CSF prophylaxis greatly reduced the IL-6 concentration in the peritoneum at the time of lavage (24 h after PCI) (1080 pg/ml with lavage alone *versus* 390 pg/ml with lavage plus G-CSF; $P < 0{\cdot}01$, Kruskal–Wallis test) (*Fig. 3b*) and also reduced the concentration of TNF-α (270 *versus* 80 pg/ml; $P < 0{\cdot}01$) (*Fig. 3d*). At 24 h after lavage (48 h after PCI), no significant difference was observed. Levels of IL-10 were not significantly different in the peritoneal fluid before or after lavage (*Fig. 3f*).

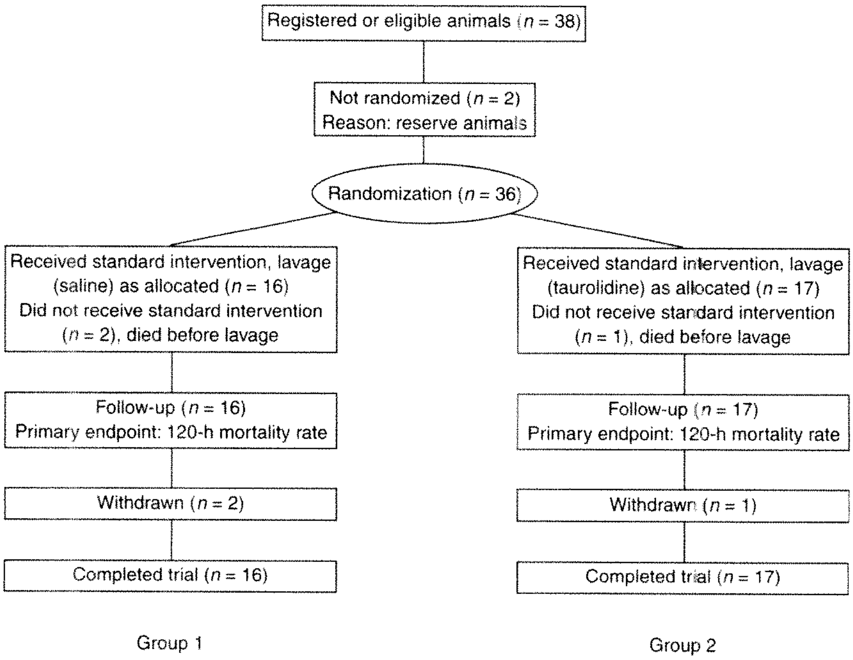

Registered or eligible animals (n = 38)
Not randomized (n = 2)
Reason: reserve animals
Randomization (n = 36)
Received standard intervention, lavage (saline) as allocated (n = 16)
Did not receive standard intervention (n = 2), died before lavage
Received standard intervention, lavage (taurolidine) as allocated (n = 17)
Did not receive standard intervention (n = 1), died before lavage
Follow-up (n = 16)
Primary endpoint: 120-h mortality rate
Follow-up (n = 17)
Primary endpoint: 120-h mortality rate
Withdrawn (n = 2)
Withdrawn (n = 1)
Completed trial (n = 16)
Completed trial (n = 17)
Group 1
Group 2

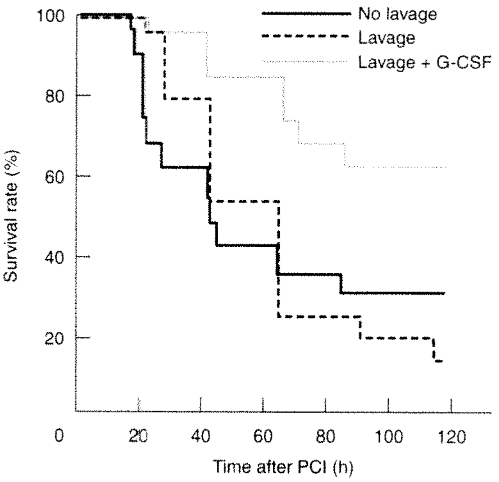
Fig. 1 Profile of trial 1, showing each step of the trial in accordance with the CONSORT statement[18] for randomized clinical trials

Trial 3: abdominal lavage with saline

No animals were withdrawn in this trial. Inspection of the abdominal cavity at the time of lavage and at autopsy revealed no difference in the degree of peritoneal surface adhesion. There was also no difference in the survival rate between the groups ($P = 0{\cdot}14$, log rank test). Sixteen of the 30 animals that had intraoperative peritoneal lavage died, compared with 11 of 30 animals that had no lavage. The analysis of equivalence with the Pearson χ^2 test showed that treatment with lavage was not as good as treatment with no lavage ($\beta = 0{\cdot}75$).

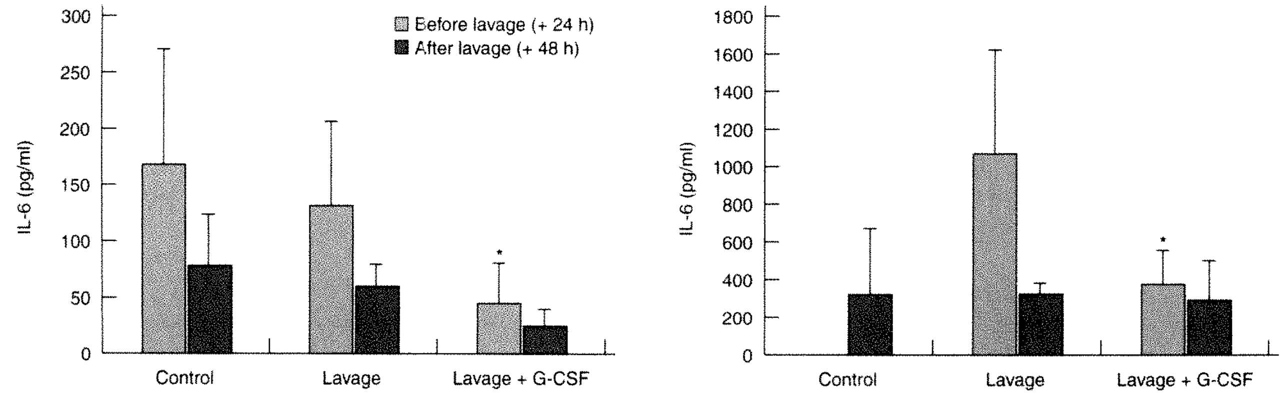
Discussion

The benefit of intraoperative peritoneal lavage is still controversial, both clinically and in laboratory experiments, as discussed in reviews by Schein *et al.*[6] and Platell *et al.*[7]. Intraoperative peritoneal lavage is performed to reduce the bacterial load and adjuvants of infections (e.g. blood, bile, faecal material) that may promote bacterial proliferation, and to wash away inflammatory mediators that may enhance local inflammation. However, lavage solutions may impair peritoneal defence mechanisms by diluting the concentration of opsonins. In the absence of opsonins, phagocytosis of bacteria takes place only on the surface and not in the solvent[25]. Dunn *et al.*[26] demonstrated that peritoneal lavage



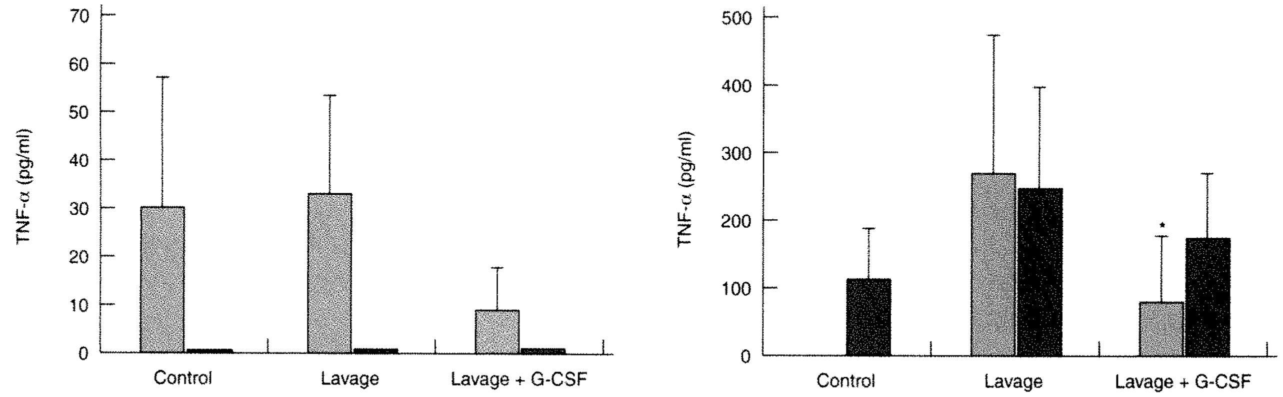
No. at risk							
No lavage	18	17	11	8	7	6	6
Lavage	18	18	14	10	5	4	3
Lavage + G-CSF	18	18	17	15	12	11	11

Fig. 2 Kaplan–Meier survival analysis over 120 h for rats in trial 2 having peritoneal contamination and infection (PCI) in a clinic modelling randomized trial with no lavage, peritoneal lavage with saline, and granulocyte colony-stimulating factor (G-CSF) prophylaxis plus lavage. All rats had antibiotic prophylaxis with co-amoxiclav 1 h before PCI. Isotonic saline at 37°C was used for peritoneal lavage 24 h after operation. $P < 0{\cdot}05$ (lavage plus G-CSF *versus* lavage and no lavage, log rank test)



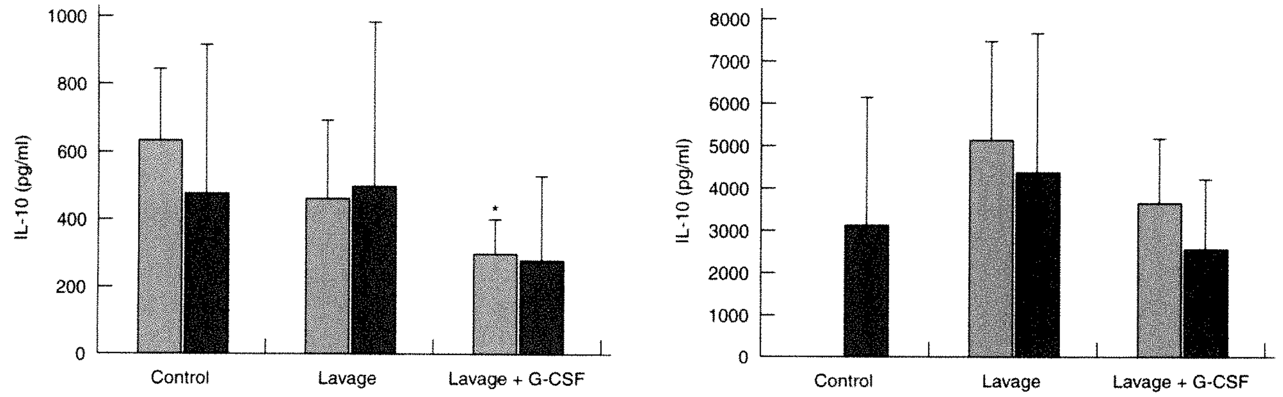
a IL-6 in plasma

b IL-6 in peritoneal fluid



c TNF-α in plasma

d TNF-α in peritoneal fluid



e IL-10 plasma

f IL-10 in peritoneal fluid

Fig. 3 Interleukin (IL) 6, tumour necrosis factor (TNF) α and IL-10 levels in plasma and peritoneal fluid of rats with and without lavage and granulocyte colony-stimulating factor (G-CSF) prophylaxis 24 and 48 h after peritoneal contamination and infection in trial 2. Determination of cytokine levels was performed by rat enzyme-linked immunosorbent assay. Values are mean(s.e.m.) (n = 9). IL-6 levels in **a** plasma (*P < 0·05 *versus* control and lavage groups, Kruskal–Wallis test) and **b** peritoneal fluid (*P < 0·01 *versus* lavage, Kruskal–Wallis test). TNF-α levels in **c** plasma and **d** peritoneal fluid (*P < 0·01 *versus* lavage, Kruskal–Wallis test). IL-10 levels in **e** plasma (*P < 0·01 *versus* control and lavage groups, Kruskal–Wallis test) and **f** peritoneal fluid

with saline increased bacterial proliferation and the 48-h mortality rate in a rat model of intra-abdominal infection.

Animal trials of intra-abdominal lavage have demonstrated either a benefit[27] or an adverse effect[28]. In contrast to these and other animal experiments, the present study included the complex clinical management of anaesthesia, volume loading, antibiotic prophylaxis in a clinically used dosage, laparotomy, contamination and infection with human stool bacteria (PCI) and postoperative analgesia under trial conditions of randomized clinical trials[19]. In contrast to the caecal ligation and puncture model, the PCI model allows a direct dose-dependent (faecal inoculum) induction of the mortality rate and the use of human bacteria with its known antibiotic resistances[19,22,29].

In many animal experiments analysing the impact of intraoperative or postoperative abdominal lavage, the importance of adequate intravenous antibiotic prophylaxis has been neglected. Trials have been performed without any antibiotic prophylaxis[30] or with a clinically unusual route of administration (e.g. intramuscular) of antibiotics[27]. In addition, pilot trials have suggested that it is important to heat lavage solutions to 37°C in order not to harm the animals, and careful lavage is required in all abdominal areas to achieve optimal removal of pus and bacteria.

There is also controversy regarding the type of lavage solution used. Some studies have demonstrated that lavage with saline[27] is as good as that with antiseptic solutions. Other trials have favoured lavage with antiseptic agents such as povidone–iodine[31] or taurolin[3]. Taurolin was claimed to be beneficial via its bacteriostatic activity[32] and positive interaction with the cytokine network, by blocking the endotoxin-induced cytokine response[33]. In the present study taurolin demonstrated no benefit, possibly because lavage solutions such as those containing taurolin induce peritoneal surface adhesions[34], which have a negative effect on the outcome. However, no differences in the grade of adhesions on the peritoneal surface were observed. Better results were suggested in multiple retrospective studies[5] and in a prospective uncontrolled clinical trial[4] when antibiotics were added to the lavage solution. However, there is no high-level evidence that lavage with antibiotics improves results in patients receiving adequate systemic antibiotics[2]. In the trials presented here more animals died in the lavage group compared with animals having no relaparotomy (trial 2) or those having reoperation with mechanical cleansing but without lavage (trial 3).

The concentration of cytokines in the peritoneal fluid is much higher than that in plasma[35]. The aim of reducing levels of proinflammatory cytokines by abdominal lavage was attained in this study, as 24 h after lavage levels of the cytokines IL-6, IL-10 and TNF-α were similar in groups with and without lavage, in both peritoneal fluid and plasma. One clinical trial[36] has shown that by only 2 h after lavage the concentrations of IL-6, IL-8, elastase and cathepsin B had returned to pretherapeutic levels in patients with peritonitis. Recent studies have suggested that endothelial cells are a potent site of cytokine production and release after stimulation with bacterial toxins[37]. Extended saline lavage also failed to reduce the mesothelial microbial content[30]. In contrast, the native microbial defence mechanisms in the peritoneum may be negatively affected by lavage, as summarized in recent reviews[38–40]. Notably, however, the phagocytic activity of granulocytes was not downregulated by abdominal lavage (trial 2).

In this study G-CSF was found to reverse the negative effect of lavage on survival by improving survival compared with that observed in animals that had no lavage. The ability of G-CSF prophylaxis to increase survival in CMRTs in which PCI was induced has been demonstrated previously[19,22,29]. Possible explanations for the increased survival seen with G-CSF prophylaxis are the stimulation of cellular immune defence mechanisms and alterations in the cytokine network. The four major functions of granulocytes in the host defence are: (1) adhesion to the endothelium (CD11b/c and CD18 expression) and extravasation, (2) chemotaxis (migration in the direction of chemokines and bacterial toxins), (3) phagocytosis of bacteria, fungi and viruses, and (4) lysis of microbes (proteases and reactive oxygen species). In previous studies it has been shown that migration, phagocytosis and production of superoxide anions are restored to normal by G-CSF prophylaxis in animals with PCI[13]. Induction of the adhesion molecules CD11b/c and CD18 on circulating granulocytes and other enhanced leucocyte functions by G-CSF have also been demonstrated[41,42]. In addition, reduced levels of proinflammatory cytokines (IL-6 and TNF-α) at the site of infection (peritoneum) and systemically may explain the increased survival in animals receiving G-CSF.

In the absence of conclusive controlled clinical trials, and given the results presented here, the value of intraoperative abdominal lavage is highly questionable. Not only may it be useless, it may even be harmful. Thus, in the guideline for the management of anastomotic leakage in the ongoing clinical trials with G-CSF[1], intraoperative lavage is not recommended. Conversely, immunostimulation with G-CSF appears to be a promising approach as a prophylactic measure in patients subjected to peritoneal contamination and who are at risk of bacterial peritonitis.

Acknowledgements

The authors thank Amgen, Munich, Germany for providing the filgrastim and additional support. Special thanks go to

Ingeborg Muttschall and Martin Middeke for laboratory work, and to Armin Demant for performing the animal trials.

This work was supported by the Deutsche Forschungsgemeinschaft (BA 1560-2/3).

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Original article

Peritoneal response to pneumoperitoneum and laparoscopic surgery

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Background: It is generally believed that laparoscopic surgery inflicts less trauma to the peritoneum than open surgery. Local peritoneal fibrinolysis is a critical factor in adhesion development. The objective was to investigate fibrinolytic changes in the peritoneum during laparoscopic and open surgery.

Methods: At laparotomy ($n = 10$) peritoneal biopsies were taken at opening of the abdomen and just before closure. At laparoscopy ($n = 12$) opening peritoneal biopsies were taken after carbon dioxide insufflation, and closure biopsies just before exsufflation. Tissue concentrations of tissue-type plasminogen activator (tPA), plasminogen activator inhibitor type 1 (PAI-1) and the resulting tPA activity were assayed.

Results: Concentrations of tPA in peritoneal tissue declined during operation in both groups, but significantly so only in the laparotomy group (– 53 per cent; $P = 0{\cdot}01$). PAI-1 levels were higher in opening biopsies from the laparoscopy group ($P = 0{\cdot}004$). There was an increase in PAI-1 concentration during laparotomy, but not during laparoscopy. At the end of the operation, there was no difference between the groups. The resulting tPA activity did not differ between groups at opening or closure. In both groups there was a significant decline during operation (laparotomy: –59 per cent, $P = 0{\cdot}02$; laparoscopy: –63 per cent, $P = 0{\cdot}01$).

Conclusion: These findings indicate that the peritoneal response to open and laparoscopic surgery is similar. The initial rise in peritoneal PAI-1 concentration during laparoscopy suggests an adverse effect of carbon dioxide insufflation, which might affect peritoneal repair.

Paper accepted 28 June 2002

British Journal of Surgery 2002, 89, 1465–1469

Introduction

Laparoscopic surgery is considered to be less traumatic than open surgery, resulting in a reduced degree of adhesion formation[1]. This, however, has been difficult to establish clinically in a convincing manner and little is known about the response of the peritoneum during laparoscopic surgery.

Local fibrinolytic activity of the peritoneum has been demonstrated to play a key role in postoperative adhesion formation caused by surgical trauma[2,3]. Fibrin is deposited at sites of injury. Local plasminogen activator activity is exerted mainly by tissue-type plasminogen activator (tPA)[4,5]; when this is sufficient, fibrin will be degraded by plasmin and fibrinous adhesions resolved. If tPA is inhibited by plasminogen activator inhibitor type 1 (PAI-1), the fibrin clot remains and adhesion formation proceeds[4,6]. PAI-1 has also been associated with local tumour invasion capacity in mice[7], which may be relevant to the debate about port-site metastasis in laparoscopic surgery.

A second plasminogen activator, urokinase plasminogen activator (uPA), is also present in the peritoneal environment[8], but is responsible for only about 5 per cent of the local fibrinolytic capacity[5]. It is associated with tissue remodelling[9], and may be important in neoplastic invasion[10–12].

This study was conducted to investigate the effect of laparoscopy on changes in the fibrinolytic system in peritoneal tissue compared with open surgery.

Patients and methods

Patients

Twenty-two patients who were scheduled for either open ($n = 10$) or laparoscopic ($n = 12$) cholecystectomy were studied. Of the ten patients recruited for open surgery, four had common bile duct stones and one had gallbladder cancer. (Groups were uneven as it was difficult to recruit patients with non-inflammatory cholelithiasis for open surgery.) The 12 laparoscopic patients had cholelithiasis diagnosed by ultrasonography with no suspicion of common bile duct stones. No patient in either group had any acute inflammatory process in the peritoneal cavity. The study was approved by the local ethics committee.

Operating procedures

Both open and laparoscopic cholecystectomies were performed as elective procedures. Open cholecystectomy was carried out through a subcostal incision. At laparoscopy, pneumoperitoneum of 14 mmHg carbon dioxide was established using a Veress needle, and maintained throughout the operation. A standard four-trocar setting with the optic port at the umbilicus and the main working port in the upper midline was used. The operating time was recorded.

Peritoneal samples

For open procedures, peritoneal biopsies were taken immediately after opening the abdomen and immediately before closure. For laparoscopic procedures, the sampling took place after carbon dioxide insufflation had been completed, and just before exsufflation. In open surgery approximately 1 cm^2 of peritoneal tissue was cut out with scissors, taking care not to include any other tissue. These biopsies were taken from the right abdominal side wall, close to the surgical site.

At laparoscopy three peritoneal biopsies were taken with a laparoscopic biopsy forceps, from a similar site as in laparotomy, and pooled. Earlier experiments had demonstrated that this amount of tissue (20–40 mg) was required for the subsequent analysis[13]. These samples, although small, were all almost free from irrelevant tissue. The amount of mechanical handling of biopsies with the different methods was judged to be similar. All biopsies were put in a test tube, snap-frozen in liquid nitrogen, and stored at – 70°C until further processing.

Tissue processing and biochemical assays

Tissue samples were weighed, then homogenized with an Ultra-Turrax homogenizer (Janke & Kunkel, Staufen, Germany). Proteins were extracted as described previously[14], and stored in aliquots at – 70°C until batch analysis.

Total tissue concentrations of tPA and PAI-1 were assayed using enzyme-linked immunosorbent assays (ELISAs) from Biopool (Umeå, Sweden). The detection limits for the ELISA kits were 1·5 and 0·5 ng/ml for tPA and PAI-1 respectively, with interassay variations of 3·5–5·4 per cent and 2·4–3·3 per cent. The intra-assay variations were 8 per cent overall. Functional tPA activity was assayed using an ELISA kit (Novo Nordisk, Bagsvaerd, Denmark), with a lower detection limit of 1 pmol/l, interassay variation of 7·8–18·0 per cent and intra-assay variation of less than 8 per cent.

Tissue uPA concentrations were assayed using an ELISA kit (Monozyme, Hoersholm, Denmark) with a detection limit of 0·05 ng/ml, an intra-assay variation of 8 per cent and interassay variation of 2·4 per cent. The total protein for each sample was analysed by a standard protein assay (DC Protein Assay; Bio-Rad, Hercules, California, USA). Results were normalized to the total protein content of each biopsy to minimize possible influences of the different sampling techniques[13].

Statistical analysis

An unpaired Mann–Whitney *U* test was used to test differences between the two treatments. A paired Wilcoxon signed rank test was used to analyse intraoperative changes. Least squares linear regression was used to investigate correlation with time.

Results

Operating time

The median duration of open surgery was 90 (range 25–240) min. In the laparoscopy group the median operating time was 120 (range 80–205) min. Laparoscopic operation took significantly longer than open surgery ($P = 0.01$).

Fibrinolytic expression in peritoneal tissue

At the beginning of the operation

The median concentrations of peritoneal tPA were the same in both groups ($P = 0.39$) (*Fig. 1*). PAI-1 expression was significantly greater in the laparoscopy group (119 per cent higher) than in the laparotomy group ($P = 0.004$) (*Fig. 2*). Functional tPA activity, however, did not differ between the two groups ($P = 0.11$) (*Fig. 3*). Peritoneal uPA concentrations were significantly higher in tissue from the laparotomy group than in that from the laparoscopy group (70 per cent higher; $P = 0.04$) (*Fig. 4*).

At conclusion of the operation

There were no differences in concentrations of tPA ($P = 0.64$) or PAI-1 ($P = 0.29$) between groups at the end

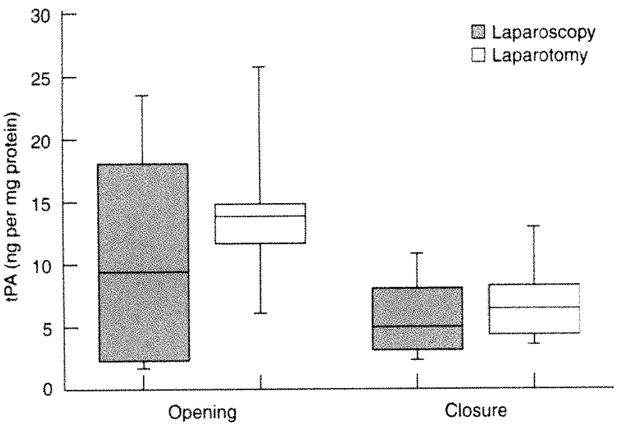

Fig. 1 Tissue-type plasminogen activator (tPA) concentration in peritoneal samples at the beginning (opening) and end (closure) of laparotomy and laparoscopy. Values are median (horizontal line), interquartile range (boxes), and 10th and 90th percentiles (error bars). There was a significant decrease during operation in the laparotomy group ($P = 0.01$), but not in the laparoscopy group ($P = 0.10$) (Wilcoxon's signed rank test). There was no difference between groups at opening ($P = 0.39$) or closure ($P = 0.64$) (unpaired Mann–Whitney *U* test)

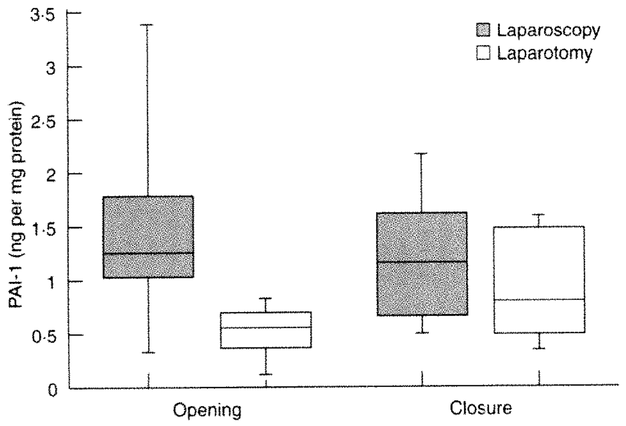

Fig. 2 Plasminogen activator inhibitor type 1 (PAI-1) concentration in peritoneal samples at the beginning (opening) and end (closure) of laparotomy and laparoscopy. Values are median (horizontal line), interquartile range (boxes), and 10th and 90th percentiles (error bars). The laparoscopy group had significantly higher levels of PAI-1 in the opening samples than the laparotomy group ($P = 0.004$; unpaired Mann–Whitney *U* test). There was a significant increase in PAI-1 concentration during laparotomy ($P = 0.05$) but not during laparoscopy ($P = 0.69$) (Wilcoxon's signed rank test). At end of surgery there was no difference between the groups ($P = 0.29$; unpaired Mann–Whitney *U* test).

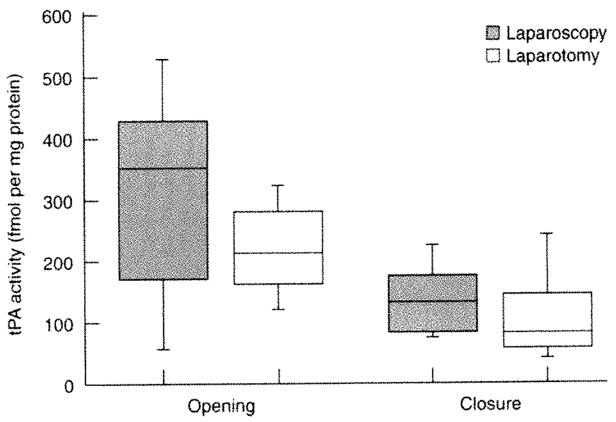

Fig. 3 Functional tissue-type plasminogen activator (tPA) activity in peritoneal samples at the beginning (opening) and end (closure) of laparotomy and laparoscopy. Values are median (horizontal line), interquartile range (boxes), and 10th and 90th percentiles (error bars). The two groups did not differ at opening ($P = 0.11$) or closure ($P = 0.17$) (unpaired Mann–Whitney *U* test). In both groups there was a significant decrease in tPA activity during operation (laparotomy: $P = 0.02$; laparoscopy: $P = 0.01$) (Wilcoxon's signed rank test)

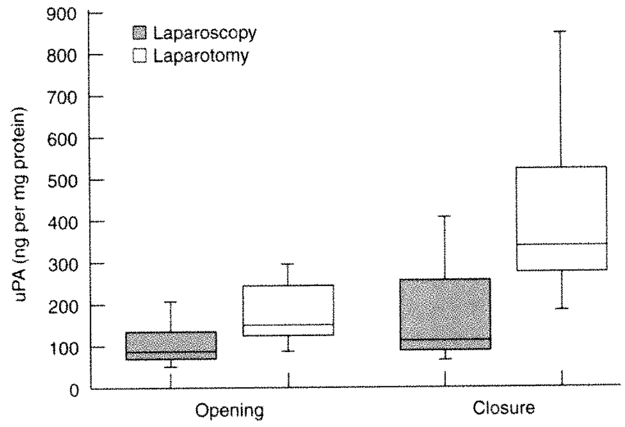

Fig. 4 Urokinase plasminogen activator (uPA) concentration in peritoneal samples at the beginning (opening) and end (closure) of laparotomy and laparoscopy. Values are median (horizontal line), interquartile range (boxes), and 10th and 90th percentiles (error bars). The laparotomy group showed significantly higher peritoneal uPA concentrations throughout operation (opening: $P = 0.04$; closure: $P = 0.02$, unpaired Mann–Whitney *U* test). This group also had an intraoperative increase in uPA concentration ($P = 0.02$) that was not found in the laparoscopy group ($P = 0.07$) (Wilcoxon's signed rank test)

of the procedures, nor did the levels of tPA activity differ ($P = 0.17$) (*Figs 1–3*). There was, however, a significant difference in uPA levels; patients who had a laparotomy had a significantly higher level of tissue uPA (197 per cent higher) than those operated on laparoscopically ($P = 0.02$) (*Fig. 4*).

Intraoperative changes

The intraoperative tPA concentration decreased significantly (– 53 per cent) in the laparotomy group ($P = 0.01$), and there was a non-significant trend for decreased tPA expression (– 45 per cent) in the laparoscopy group ($P = 0.10$) (*Fig. 1*). In contrast, PAI-1 concentrations increased significantly during operation in the laparotomy group (+ 47 per cent; $P = 0.05$), but not in the laparoscopy group ($P = 0.69$) (*Fig. 2*). The resulting tPA activity declined significantly, and in a similar manner, in both groups. Peritoneal tPA activity declined by 59 per cent in patients who had a laparotomy ($P = 0.02$) (*Fig. 3*) and by 63 per cent in those who had laparoscopy ($P = 0.01$) (*Fig. 3*). Tissue uPA concentration tended to increase during operation (+ 27 per cent), but not significantly so ($P = 0.07$) in the laparoscopy group. In the laparotomy group, however, the uPA concentration increased markedly (+ 122 per cent) ($P = 0.02$) (*Fig. 4*).

Correlation with operating time

In the laparoscopy group there was a significant correlation between operating time and the intraoperative decrease in peritoneal tPA activity ($r = 0.71$, $P = 0.01$). In the laparotomy group there was no such correlation ($r = 0.18$, $P = 0.61$). Intraoperative changes in tPA and PAI-1 levels showed no correlation with operating time in either of the treatment groups. The intraoperative increase in uPA level correlated significantly with operating time in the laparotomy group ($r = 0.85$, $P = 0.01$) but not in the laparoscopy group ($r = 0.26$, $P = 0.42$).

Discussion

The present findings indicate that there is a differential response to abdominal entry and the establishment of a pneumoperitoneum, resulting in increased PAI-1 concentrations and lowered uPA concentrations in laparoscopic surgery, compared with laparotomy. Once the operation commenced, the peritoneal fibrinolytic response was similar in the two groups, albeit more pronounced in the laparotomy group.

The present finding of significantly raised PAI-1 concentrations and decreased uPA concentrations immediately after carbon dioxide insufflation suggests that the insufflation procedure provokes a peritoneal response. Although the present study does not address this question directly, it is reasonable to assume that either the carbon dioxide, the flow of gas, or peritoneal distension alone or in concert, triggered this response. Gray *et al.*[15] have shown that cold, dry gas with a high insufflation speed creates a 'super jet cooling' effect on the peritoneal surface, leading to desiccation and cell injury. This injury could potentially promote release of PAI-1.

There is an ongoing debate about whether laparoscopy should be used for cancer surgery, following reports of increased peritoneal tumour implantation and port-site metastasis[16,17]. The present observation of an early post-insufflational increase in peritoneal PAI-1 and sustained high levels throughout operation might be of interest, although it should be noted that levels were similar in both groups by the end of the operation. The absence of host PAI-1 has been demonstrated to prevent cancer invasion[7], and the role of PAI-1 in cell adhesion regulation is currently under investigation[18].

In the present study peritoneal uPA concentrations were consistently lower during laparoscopy than laparotomy, while a significant intraoperative increase occurred only at laparotomy. Raised uPA concentrations have been associated with inflammatory conditions of the peritoneum[6], and it is possible that laparoscopic and conventional surgery elicit different degrees of inflammation in the peritoneal cavity. Ivarsson *et al.*[19] found that cultured human mesothelial cells stimulated with tumour necrosis factor (TNF) α showed an increased secretion of PAI-1, but that secretion of uPA was not affected. Krahenbuhl *et al.*[20], comparing open and laparoscopic fundoplication in rats, found an early peroperative rise in plasma TNF-α levels in the laparoscopy group, but not during laparotomy. This observation suggests that there was an initial peritoneal response to pneumoperitoneum, in accordance with the present observations, and that TNF-α might mediate this process.

Studies of adhesion formation after open and laparoscopic surgery have been made in animal models and clinical trials[1,20,21]. Laparoscopic procedures seem to induce fewer adhesions and adhesions of less severity, although Duron and co-workers[22] found that adhesions resulting from laparoscopic procedures gave rise to bowel obstruction to the same extent as those resulting from open surgery.

Peritoneal fibrin-clearing capacity is pivotal in the early formation of adhesions[2]. tPA and its inhibitor PAI-1 closely coordinate regulation of peritoneal fibrinolytic capacity. In the present study the intraoperative decline in tPA concentration was significant only in the laparotomy group, indicating that a comparable laparoscopic operation created a less severe peritoneal injury. However, this advantage was counteracted by the initial increase in peritoneal PAI-1 concentration in the laparoscopically operated patients, resulting in a similar net peritoneal tPA activity in the two groups, indicating an equal adhesiogenic situation. The more severe adhesions seen after open surgery may be due to more pronounced handling of intra-abdominal viscera, leading to mesothelial cell abrasion and local sites of trauma.

The intraoperative decline in tPA activity correlated with operating time of laparoscopy, but not of laparotomy. That operating time at laparoscopy can influence outcome has been shown in previous studies, in which the duration of the laparoscopic procedure correlated with increasing systemic acidosis[23] and with increasing adhesion score[24]. Thus, laparoscopic procedures may have a unique element of ongoing peritoneal trauma related to the length of the procedure.

It seems that the establishment of carbon dioxide pneumoperitoneum causes a specific local peritoneal response that could influence tumour growth and be adhesiogenic. The mechanism remains to be investigated, but the peritoneal response to carbon dioxide insufflation and carbon dioxide pneumoperitoneum merits further examination.

Acknowledgements

This study was supported by the Gothenburg Medical Society and the Swedish Medical Research Council (project no. K2000-32X-12650).

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Original article

Model for experimental revascularized laryngeal allotransplantation

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Background: Although a human laryngeal transplant has been undertaken successfully, important questions remain that require a suitable animal model.

Methods: A pig model for allotransplantation has been developed. Organ perfusion was studied in nine animals before four transplants were performed in congenic (unrecovered) animals and eight in unmatched (recovered) animals. Larynges were regularly examined endoscopically until death at 14 days. Immunosuppression included the use of tacrolimus. Revascularization was achieved by anastomosing the donor right cervical vascular tree to the recipient common carotid. In recovered animals, four allografts were placed orthotopically and four heterotopically.

Results: The pig larynx was perfused adequately via the right cervical vascular tree and congenic grafts were well tolerated. Of eight allografts, seven were well tolerated and remained healthy for the duration of the study (14 days). One allograft became infected between days 4 and 7 after operation. Median operating time was 6 h, with a median cold ischaemia time of 3 h.

Conclusion: Revascularized allotransplants of the larynx can be undertaken reliably in pigs and this provides a preclinical model for studies of laryngeal transplantation.

Presented in part to the 22nd Midwinter Research Meeting of the Association for Research in Otolaryngology, St Petersburg Beach, Florida, USA, February 1999

Paper accepted 20 June 2002

British Journal of Surgery 2002, **89**, 1470–1475

Introduction

Laryngeal transplantation is now a reality in humans[1,2]. However, there are many questions still outstanding before full clinical trials may be proposed. The laryngeal mucosa is rich in organized immune tissue, larynx-associated lymphoid tissue[2–4], which may render it sensitive to immunological responses upon revascularization (both ischaemia–reperfusion injury and rejection), and the degree to which immunosuppression may be withdrawn across varying antigenic boundaries needs to be established. Also, the issue of mobilizing the vocal cords, and thus removing the need for tracheostomy, remains an important one.

Important steps have been taken in our understanding of laryngeal neurology in dog and cat models. However, these animals have significant drawbacks in the transplant setting. A rat model has been adopted successfully to explore questions such as choice of reperfusion solution and immunosuppressant, but again this model has some limitations, not all of which are size related.

It has been shown that pig laryngeal mucosal immunology has considerable homology to that of humans[4–6]. Also, the pig larynx is similar anatomically[6] and its size allows orthotopic transplantation with the opportunity for repeated endoscopic examination and biopsy. Pigs are more tolerant of immunosuppression than any other animal, and have been used extensively in recent decades to study the transplantation of other organs[7–9]. This experience means that long-term survival of such transplant recipients is possible, which is ideal for reinnervation studies of the larynx. In addition, there is a broader range of immunological probes available to study the immune response of the pig[10] and a variety of strains is available, including fully major histocompatibility complex (MHC) inbred and congenic strains, making studies of a complete range of antigenic challenges possible[11]. The aim of the

Table 1 Characteristics of animals used in each experiment

	Procedure 1	Procedure 2	Procedure 3
Experiment	Graft retrieval	Laryngeal transplantation in congenic animals	Laryngeal allografting and recovery
No. of pigs	9	8	8 (orthotopic) 8 (heterotopic)
Breed	Large White–Landrace hybrids	Minnesota minipigs	Large White–Landrace hybrids
Median (range) weight (kg)	22 (20–25)	12 (10–15)	22 (20–25)
Age (weeks)	20–24	10	21

present study was to develop a porcine model of revascularized laryngeal allotransplantation.

Materials and methods

Enzootic pneumonia-free Large White–Landrace hybrids (median weight 22 kg, age 20–24 weeks, obtained from Charles River, France and Institute of Animal Health (IAH), Compton, UK) and Minnesota minipigs (median weight 12 kg, age 10 weeks, obtained from IAH) were employed for the study. No tissue-typing was performed on the Large White hybrids, but they were not litter mates and only distantly related. Minnesota minipigs are specifically inbred for the MHC loci, here c/c haplotype (*Table 1*). The studies were carried out in accordance with national regulations (Home Office) and were approved by the Research Ethics Boards of both Bristol and Hanover Medical Schools.

Graft retrieval

In pigs, the main blood supply to the larynx comes from the right-sided vessels[9] and so the first objective was to preserve the vascular supply from the right thyroid arteries, branches of the right subclavian artery and external carotid artery. The study was undertaken in nine fresh pig cadavers, heparinized immediately before death (heparin sulphate 5 mg/kg intravenously). Through a midline incision and a median cervicosternotomy, the vessels between the mediastinum and limbs and the azygos veins were ligated distally. Main arteries were looped to control, the aorta was cross-clamped and the graft perfused with saline via the aortic root (demonstrated by blanching of thyroid gland). The larynx and trachea were then raised *en bloc* and the adequacy of perfusion was further tested by the infusion of 10 per cent methylene blue dye in sterile water via the perfusing cannula (*Fig. 1*). After this, grafts were preserved in formalin and dissected to study the neuromuscular anatomy.

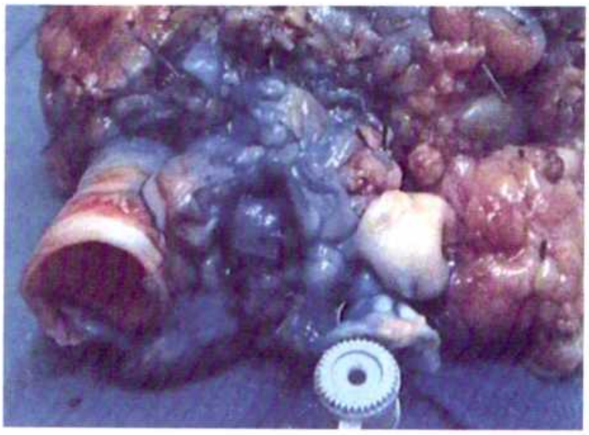

Fig. 1 Isolated larynx perfused with 10 per cent methylene blue via a cannula in the right innominate artery, showing perfusion of major and minor vessels. Free flow of dye from the vena cava can be seen

Laryngeal transplantation in congenic animals

Eight Minnesota minipigs were premedicated with ketamine 10 mg/kg (Ketamin® Gräub; Albrecht, Aulendorf, Germany), azaparone 2 mg/kg (Stresnil®; Janssen-Cilag, Neuss, Germany) and buprenorphine 10 µg/kg (Temgesic™; Essex Pharma, Munich, Germany), all given intramuscularly, induced with propofol 2–4 mg/kg intravenously (Propofol-Lipuro™ 1 per cent; B. Braun, Melsungen, Germany) and maintained on isoflurane (Forene®; Abbott, Wiesbaden, Germany) in oxygen with intermittent bolus administration of fentanyl (Fentanyl®-Janssen; Janssen-Cilag), midazolam (Dormicum® 5; Roche, Grenzach-Wyhlen, Germany) and atracurium (Tracrium®; GlaxoWellcome, Bad Oldesloe, Germany).

The larynx and trachea were retrieved using the above-mentioned technique, except that heparin 5 mg/kg was administered immediately before the aorta was cannulated with an aortic root cannula (DLP, Grand Rapids, Michigan, USA) through which University of Wisconsin solution was infused (65 ml/kg at 4°C at a perfusion pressure of 80 mmHg). The graft was placed in cold (4°C) storage.

In heparinized recipient animals, the right common carotid artery was divided, after which the donor subclavian artery (with thyroid arteries) was interposed. The graft was reperfused after intravenous injection of 240 mg methylprednisolone acetate, and the venous loop was closed with

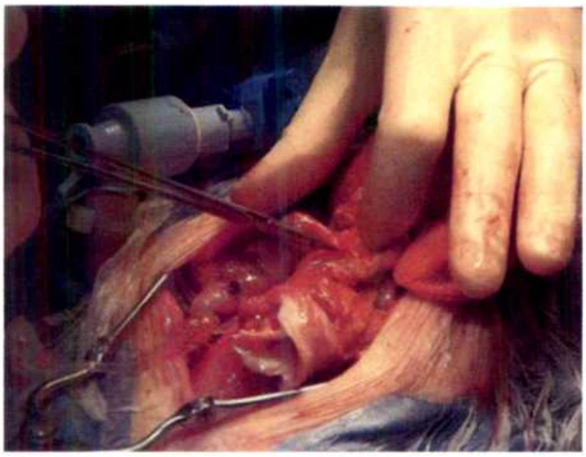

Fig. 2 The graft is 'railroaded' into the host pharynx with a series of polyglactin sutures. An arterial pressure monitor is in place in the left common carotid; this does not affect the largely right-sided flow to the graft

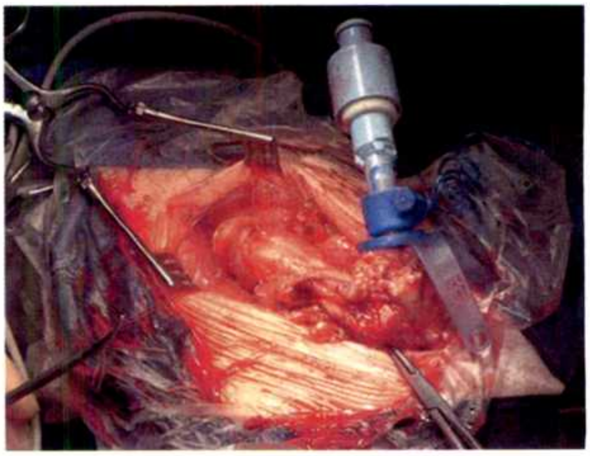

Fig. 3 Orthotopic laryngeal graft in place before closure. Normal purple colour has returned to the thyroid (centre field), indicating successful reperfusion. A tracheostomy is placed in the recipient trachea

anastomosis of the recipient right brachiocephalic venous trunk to the donor vena cava. Allograft hypothermia was maintained by topical application of cold saline solution.

Recipient laryngectomy was performed, preserving the surrounding vascular tree and thyroid gland. The donor larynx was placed orthotopically (*Figs 2* and *3*) via repair of pharyngeal constrictor muscles in two layers (*Fig. 3* and *4*), while caudally the trachea was repaired with a short overlapping segment.

After operation the animals were maintained under anaesthesia for 8 h to evaluate physiological parameters before the experiment was terminated. Graft perfusion was monitored by direct observation and measurement of laser Doppler flux (Flolab®; Moor Instruments, Axminster, UK) via a rigid laryngoscope (Karl Storz, Tuttlingen, Germany). Mucosal biopsies were snap-frozen and processed for multiple-colour immunofluorescence to look for MHC expression.

Laryngeal allografting and recovery

Group 1: orthotopic placement

Laryngeal transplantation was performed as described above between four pairs of unmatched female Large White hybrids. At completion of the procedure, a tracheostomy was created based on the recipient trachea and a T-tube stent placed through the tracheal anastomosis. A feeding gastrostomy was performed via minilaparotomy, and animals recovered.

Group 2: heterotopic placement

In four pairs of unmatched female Large White hybrids the same procedure was performed except that the recipient larynx was left *in situ*. The donor larynx was placed without tension on the vascular anastomoses, and proximal and distal apertures were created in the cervical skin. The orifices of the laryngeal and tracheal grafts were then anastomosed to these apertures. No attempt was made to repair the laryngeal nerves in this study.

After operation all pigs were given tacrolimus 0·3 mg/kg daily intramuscularly (Prograf®; Fujisawa, London, UK) and prednisolone 2 mg/kg per day. The larynx and trachea were examined endoscopically on day 1 and every 3 days until death at 14 days. Post-mortem larynges were examined grossly and microscopically.

Results

In the cadaver study, median operating time improved from an initial 4·5 h to a consistent 3 h; consistent perfusion was obtained only in the last six animals. The use of methylene blue dye confirmed that the blood supply of the larynx was well supported by the right vascular tree alone (*Fig. 1*). Dissection of the recurrent laryngeal nerve demonstrated a consistent, easily identifiable, branch to the posterior cricoarytenoid muscle (*Fig. 4*). Distribution of other nerves and muscles was broadly similar to that in humans.

In the non-recovery experiment, anaesthesia was well tolerated for 8 h and all grafts were perfused adequately for the duration of the study. Laser Doppler assessment showed near-normal (preretrieval) levels of mucosal blood flux (at least 80 arbitrary units) throughout. Many cells expressing MHC class II antigens were observed in laryngeal mucosal biopsies (*Fig. 5*). These were in both the epithelium and the lamina propria, and many had 'dendritic' morphology.

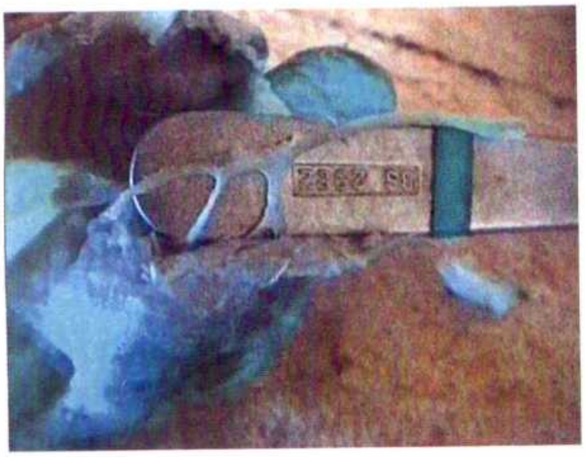

Fig. 4 Dissection of larynx perfused with 10 per cent methylene blue to show the main trunk of the recurrent laryngeal nerve dividing into three main branches. The first (most caudal) branch is that to the posterior cricoarytenoid and is suitable for studies of motor reinnervation

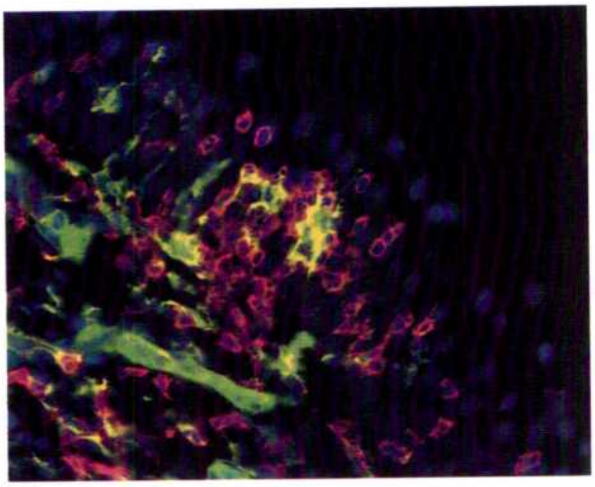

Fig. 5 Multiple-colour immunofluorescence image of laryngeal graft mucosa showing major histocompatibility complex (MHC) class II-positive cells (capable of antigen presentation; green) amid CD45-positive cells (common leucocyte antigen; red). Nuclear staining is with DAPII (blue). There are frequent MHC class II-positive cells in both epithelium and lamina propria, suggesting a capacity for vigorous antigen presentation to recipient T cells. The morphology of some of these cells suggests that they are dendritic cells. Pig-specific monoclonal antibodies were used

In the transplant series, median operating time was 6 (range 5–7·5) h, with a median cold ischaemia time of 3 (range 2·5–4·5) h; there were no differences between the groups.

In the four animals receiving orthotopic transplants, one graft became infected between day 4 and day 7. The other grafts were well tolerated to 14 days and at autopsy there was no aspiration pneumonia, the three larynges being macroscopically normal with no evidence of mucosal loss or oedema. Microscopically, there was mild lymphocytic infiltration in two of three grafts, and no evidence of muscle loss or reduction in cilia in any of the grafts, compared with the normal pig larynx.

In the heterotopic group all four grafts and pigs remained healthy when examined clinically and endoscopically. At autopsy there was no aspiration pneumonia and microscopic appearances were identical to those in the previous group.

Discussion

This study shows that laryngeal transplantation in pigs can be undertaken reliably and successfully. The grafts are accepted not only by syngeneic animals, but also, with conventional immunosuppression, between antigenically dissimilar animals.

There remains no good alternative to laryngectomy for patients with irreversible disease of the larynx. Despite the perceived success of laryngectomy as a treatment for advanced laryngeal cancer and the great strides made in rehabilitation, the operation is associated with significant morbidity. Laryngeal transplantation could offer the potential for a near-normal quality of life[1,2], but the techniques have to be verified in an appropriate animal model.

These animals tolerate immunosuppressive agents well and there is extensive experience with transplantation of other organs[7], including lung, bronchus[8] and trachea[9]. Pigs, specifically the Minnesota minipig, are available in a variety of allelotypes, and there is a wider range of monoclonal antibodies against leucocyte antigens than in other large monogastric species.

Whilst graft and animal survival rates in this heterotopic rat model[12,13] are impressively high, the graft has to form a closed tube with the risk of alterations in the mucosal architecture, an important confounding factor in the interpretation of immunological injury in such grafts. The validity of comparing mucosal appearances with those of open-ended 'control' larynges is therefore open to question. This problem is overcome in the porcine model. Another disadvantage of the rat is the difficulty of performing reinnervation experiments.

The present orthotopic technique permits observation of a transplanted larynx in its natural position within the airway, with preservation of normal physiology, and is an ideal model for reinnervation experiments. The presence of a tracheostomy, although an essential protective measure, may theoretically increase the incidence of pulmonary and local infection, although there was little sign of this complication at 2 weeks. The situation exactly mimics planned human transplants.

The advantage of the heterotopic model is that both tracheostomy and gastrostomy are avoided, and the immunology and perfusion status of the graft can be assessed by fibreoptics and biopsy. It needs to be established that no significant differences in mucosal immunology exist between the orthotopic and heterotopic models.

Preliminary immunofluorescence studies of graft mucosa show a high degree of expression of MHC class II antigen in graft biopsies, demonstrating that MHC expression can readily be studied in this model, and suggesting that laryngeal grafts may reject quite strongly in the absence of immunosuppression. Detailed studies of the laryngeal mucosal immune response to transplantation are in progress.

The success of all three stages also raises the possibility of performing studies in an *ex vivo* perfused model, as has been successfully employed for other airway grafts[14]. Thus, isolated grafts could be exposed to a range of ischaemic and immunological insults, and the effects of therapeutic interventions against these measured, without the need to use a second animal. The best strategies screened in this way could then be tested in the full transplant model as described above.

Dogs and cats have been used successfully in studies of laryngeal reinnervation[15,16], but early laryngeal transplants in dogs were associated with high rates of mortality and graft loss[17–19]. In rat laryngeal transplants there is a 41 per cent (30 day) mortality rate[11,12], and dogs have a perioperative mortality rate of 30 per cent[9] to 75 per cent[8]. Pigs are more reliable and can be maintained economically for many months after major intervention[8,11]. Thus, the longitudinal studies required for reinnervation of laryngeal allografts are entirely feasible in the pig.

Restoration of motor function of laryngeal allografts depends on appropriate abduction of the vocal cords, achieved by reinnervating the posterior cricoarytenoid muscle[20]. Here, this muscle is supplied by a clearly identifiable branch from the recurrent laryngeal nerve, making reinnervation strategies, such as those employing phrenic nerve roots[15,16], entirely feasible. It was not the intention of the present study to examine reinnervation in detail, as this is being addressed by other work in progress.

The present technique is the first to attempt dual revascularization, using both cranial and caudal thyroid arteries, and is similar to the technique likely to be used in human trials[1].

In summary, this model is suitable for exploring the major questions still confronting laryngeal transplantation, in particular those surrounding transplantation across varying antigenic barriers, the effects of reperfusion injury, and the effectiveness of reinnervation strategies.

Acknowledgements

The authors would like to thank the teams at the Tierlaboratory, Hanover Medical School, Germany, and the thoracic surgical laboratory, Hôpital Marie Lannelongue, Paris (in particular Michel Mazmanian and Chantall Verriest). Dr Melanie Knight gave invaluable help with the identification of nerve anatomy. The administrative assistance of Mrs Eva Hicks was invaluable, whilst kind assistance with travelling expenses and drugs from Fujisawa made the collaboration possible. The authors also thank Karl Storz, Germany, for the loan of endoscopic equipment.

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Original article

Chronic pain after laparoscopic and open mesh repair of groin hernia

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Background: The aim of this study was to compare the incidence of chronic pain or discomfort after laparoscopic totally extraperitoneal (TEP) repair and open mesh repair of groin hernia, and to assess the impact of such pain on patients' physical activity.

Methods: A postal questionnaire was sent to patients who had TEP or open mesh repair of groin hernia between January 1998 and December 1999. The patients were asked about any persistent pain or discomfort in relation to the groin hernia repair and whether this pain or discomfort restricted their ability to undertake physical or sporting activity.

Results: Of the 560 available patients 454 (81·1 per cent) replied. Laparoscopic TEP repair was performed in 240 patients (52·9 per cent) and open mesh repair in 214 (47·1 per cent). Of the 454 patients, 136 (30·0 per cent) reported chronic groin pain or discomfort, which was significantly more common after open repair than after laparoscopic repair (38·3 *versus* 22·5 per cent; $P < 0{\cdot}01$). Chronic groin pain or discomfort restricted daily physical or sporting activity in 18·1 per cent of the patients. The patients who had open repair complained of significantly more restriction of daily physical activity than patients who underwent laparoscopic repair (walking, $P < 0{\cdot}05$; lifting a bag of groceries, $P < 0{\cdot}01$).

Conclusion: Chronic pain or discomfort was reported by 30·0 per cent of patients after groin hernia repair and was significantly more common after open mesh repair than after laparoscopic TEP repair. It restricted physical or sporting activities in 18·1 per cent of the patients and significantly more so after open mesh repair.

Presented in part to the Association of Surgeons of Great Britain and Ireland in Birmingham, UK, April 2001 and the Ninth International Congress of the European Association of Endoscopic Surgery in Maastricht, The Netherlands, June 2001; and published in abstract form as *Br J Surg* 2001; **88**(Suppl 1): 81

Paper accepted 11 July 2002

British Journal of Surgery 2002, **89**, 1476–1479

Introduction

Groin hernia repair is a common surgical procedure and postoperative recovery is uncomplicated in most patients. Some patients, however, continue to complain of chronic groin pain or discomfort (CGP) for months or even years after hernia repair, a complication that is becoming increasingly recognized as a significant cause of morbidity after groin hernia surgery. The reported incidence of such pain after hernia repair is thought to be about 10 per cent but varies in different studies from 0 to 60 per cent[1–3]. Several risk factors associated with CGP have been identified, including recurrent hernia repair[4], insurance status of the patient[5], day surgery[6], patient's age less than 60 years[2,6], and severe early postoperative pain[4]. The influence of surgical technique on the development of CGP remains unclear. In 1990s two techniques of groin hernia repair became popular, open mesh repair (Lichtenstein) and laparoscopic repair. Laparoscopic repairs are known to be less painful than open repairs in the early postoperative period[7]. It is not clear, however, whether laparoscopic repairs are less likely to cause CGP; some reports have noted significantly less CGP after laparoscopic than open repairs[8,9], while others have not[2,10].

The aim of this study was to compare the incidence of CGP after laparoscopic totally extraperitoneal (TEP) repair with that after open mesh repair, and to assess the impact of such pain or discomfort on patients' physical and sporting activity.

Patients and methods

The Lothian Surgical Audit Database was accessed to obtain a list of all patients who had elective groin hernia

Table 1 Hernia follow-up questionnaire

1.	Do you presently have any pain or discomfort in relation to the hernia repair? *(please circle appropriate answer)*	Pain/Discomfort/No pain or discomfort
2.	Do you have pain/discomfort related to the hernia repair?	Occasionally/Most days/Every day of the week
3.	Where is the pain?	
	Around the scar of hernia repair	Yes/No
	In the groin and shooting towards thigh	Yes/No
	In the testicles (if male)	Yes/No
	Other (specify)..	
4.	How much does this pain interfere in:	
	Walking more than a mile:	No problem/Yes, limits a little/Yes, very limiting
	Lifting or carrying groceries:	No problem/Yes, limits a little/Yes, very limiting
	Sporting activities such as playing golf, bowling, etc.:	No problem/Yes, limits a little/Yes, very limiting
	Vigorous activities such as lifting heavy objects or strenuous sports:	No problem/Yes, limits a little/Yes, very limiting

repair with a prosthetic mesh at the Western General Hospital, Edinburgh between January 1998 and December 1999. These patients were sent a postal questionnaire concerning any pain or discomfort related to the groin hernia repair and if it interfered with daily physical or sporting activity such as walking, lifting a bag of groceries, playing golf or more strenuous sports such as jogging and football (*Table 1*). The questionnaire was sent 8–32 months after surgery. Patients who did not reply were sent a second questionnaire. The data were stored on dBase™ (Ashton-Tate Corporation, Twyford, UK).

It is the authors' practice to recommend repair of a clinically demonstrable groin hernia, except in an elderly patient with a small reducible direct inguinal hernia. Laparoscopic TEP repair was performed under general anaesthesia and without fixing the Prolene (Ethicon, Edinburgh, UK) mesh in the preperitoneal space. Open mesh repair was performed by the Lichtenstein technique under general anaesthesia, except in patients with significant cardiorespiratory disease or those who preferred to have local anaesthesia. Postoperative analgesia was prescribed at the discretion of the operating surgeon or the patient's general practitioner after discharge from hospital. CGP was defined as groin pain or discomfort lasting more than 3 months after groin hernia repair[11].

The significance of differences between patients who had laparoscopic TEP repair or open repair was calculated using χ^2 test with Yates' correction.

Results

A postal questionnaire was sent to 560 patients, of whom 53·6 per cent had laparoscopic TEP repair and 46·4 per cent had open mesh repair of groin hernia. Of the 560 patients, 454 (81·1 per cent) replied; 33 (5·9 per cent) had died from causes unrelated to hernia repair and 73 (13·0 per cent) did not respond. Of the 454 patients, 240 (52·9 per cent) had laparoscopic TEP and 214 (47·1 per cent) had open mesh repair. The age and sex distribution was similar in the two groups, as was the proportion of patients in each group having repair for recurrent hernia (*Table 2*). The response rate to the questionnaire was also similar in the two groups: 80·0 per cent of patients with laparoscopic TEP repair and 82·3 per cent of patients with open repair replied. The laparoscopic group had a significantly higher proportion of patients with bilateral hernia than the open group but their small numbers did not alter the final outcome. Mean follow-up was 21 (range 8–32) months.

Table 2 Demographic details and type of hernia in 454 patients who had mesh repair of groin hernia

	Laparoscopic TEP repair (n = 240)	Open mesh repair (n = 214)
Sex ratio (M : F)	232 : 8	204 : 10
Mean age (range) years	60 (20–95)	66 (18–95)
Recurrent hernia*	25 (10·4)	25 (11·7)
Bilateral hernia*	11 (4·6)	2 (0·1)†

TEP, totally extraperitoneal. *Values in parentheses are percentages. †P < 0·05 *versus* laparoscopic (χ^2 test with Yates' correction)

Overall, chronic groin pain or discomfort was reported by 136 (30·0 per cent) of the 454 patients. Of these 34 (7·5 per cent) described pain while 102 (22·5 per cent) reported only discomfort. CGP was significantly more common after open mesh repair than after laparoscopic TEP repair (*Table 3*).

CGP restricted daily physical or sporting activity in 82 (18·1 per cent) of the patients. Patients with open repair reported significantly more restriction of daily physical activity than those who had laparoscopic repair. Restriction in sporting and vigorous activity was less after laparoscopic repair but not significantly so (*Table 4*).

The data did not allow reliable assessment of influence of grade of the operating surgeon on CGP.

Table 3 Chronic groin pain or discomfort after repair of groin hernia

	Laparoscopic TEP repair ($n = 240$)	Open mesh repair ($n = 214$)
Chronic pain or discomfort	54 (22·5)	82 (38·3)*
Chronic groin pain	10 (4·2)	24 (11·2)*
Chronic groin discomfort	44 (18·3)	58 (27·1)†

Values in parentheses are percentages. TEP, totally extraperitoneal. *$P < 0·01$, †$P < 0·05$ *versus* laparoscopic (χ^2 test with Yates' correction)

Table 4 Patients reporting restriction of physical or sporting activity due to chronic pain or discomfort after laparoscopic totally extraperitoneal and open mesh repair of groin hernia

	Laparoscopic TEP repair ($n = 240$)	Open mesh repair ($n = 214$)
Walking	17 (7·1)	29 (13·6)*
Lifting a bag of groceries	18 (7·5)	36 (16·8)†
Sports	19 (7·9)	23 (10·7)
Vigorous activity	36 (15·0)	46 (21·5)

Values in parentheses are percentages. TEP, totally extraperitoneal. *$P < 0·05$, †$P < 0·01$ *versus* laparoscopic (χ^2 test with Yates' correction)

Discussion

To the authors' knowledge, this is the first audit to specifically compare the incidence of GGP after laparoscopic TEP repair and Lichtenstein open mesh repair, the two operations for groin hernia repair recommended by the National Institute of Clinical Excellence in England and Wales[12].

Use of 'pain' or 'discomfort' as separate terms was determined by patients' use of the two terms to differentiate the severity of nociception. This study shows that 30·0 per cent of the patients had developed CGP after a mean of 21 months after hernia repair. This is strikingly similar to the 30 per cent incidence of CGP reported recently by both Bay-Nielsen *et al.*[2] and Poobalan *et al.*[6] in studies that included non-mesh repairs. In the present study CGP was significantly more common after open mesh repair than laparoscopic TEP repair. The Medical Research Council (MRC) trial[8] reported a significantly higher incidence of CGP after open repair than after laparoscopic repair (37 *versus* 29 per cent) at 1 year. The MRC trial, however, included non-mesh repairs in the open group and transabdominal preperitoneal and TEP repairs in the laparoscopic group. In a meta-analysis of randomized controlled trials of laparoscopic and open prosthetic mesh repair of groin hernia, EU Trialists found that CGP is less likely to occur after laparoscopic repair than after open repair[13]. However, they had reservations about this finding because of a lack of uniform definition of CGP in these trials. Heikkinen *et al.*[14] also reported a higher incidence of CGP after open mesh repair than after TEP repair (30 *versus* 4·5 per cent) but the follow-up was only 2 months, which is too short to assess chronic pain. In a randomized trial reported by Wright *et al.*[15] there was no significant difference between CGP after laparoscopic TEP and open repairs, but testicular pain was reported significantly more often after laparoscopic TEP repair.

CGP restricted daily physical or sporting activities in 18·1 per cent of the present patients after groin hernia repair. The impact of CGP on patients' daily physical or sporting activity is a matter of concern as these patients felt uncomfortable carrying a bag of groceries or playing sports such as golf. The patients with open repair were more likely to be affected than patients with laparoscopic TEP repair. Two recently published studies reported that up 60 per cent of patients with pain were unable to enjoy social or leisure activity 1 year after groin hernia repair[2,6].

There is increasing speculation about the cause of chronic groin pain and why laparoscopic repair appears to be superior to open mesh repair in this context. One possible explanation for neuropathic pain is injury to the ilioinguinal, iliohypogastric or genitofemoral nerves, either during exposure of the inguinal canal or handling of the cord and dissection of the hernia sac in open surgery. Lichtenstein *et al.*[16] recommended preserving the nerves in the inguinal canal to minimize the incidence of CGP. Sometimes this is difficult as the nerves may hinder the dissection or may lie across the prosthetic mesh on the posterior inguinal wall; in such circumstances some surgeons prefer to divide these nerves. In one study dividing the inguinal nerves did not reduce the incidence of CGP[17]. The genitofemoral nerve may also be at risk when the prosthetic mesh is secured in a continuous suture along the inguinal ligament or when the external spermatic vessels are divided to skeletonize the cord[18]. The authors' practice is to preserve these nerves whenever possible or to formally divide them when necessary[19]. The laparoscopic repair has the advantage of minimal access and less traumatic dissection to free the sac from the inguinal canal. Some risk factors such as staple pain[20] associated with persistent postoperative pain after laparoscopic repair are not applicable to the present study because the mesh was not fixed.

It has been argued that prosthetic mesh may contribute to the development of CGP[21]. However, the EU Hernia Trialists' systematic review found that mesh repairs are less likely to cause CGP than non-mesh repairs[22].

The implication of this study is that patients should be informed about the risk of developing CGP after groin hernia repair as this may influence their choice of laparoscopic or open repair. Further detailed studies are required to elucidate the causes and natural history of CGP, including any correlation between preoperative pain, anaesthetic technique and postoperative analgesic requirements. Furthermore, patients with CGP should be examined to determine if the pain is neuropathic or nociceptive in nature, as this may allow specific therapy to be targeted[23]. Such studies should help in the development of a strategy to treat and even prevent this disabling complication of groin hernia repair.

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Correspondence

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Randomized clinical trial comparing loop ileostomy and loop transverse colostomy for faecal diversion following total mesorectal excision (*Br J Surg* 2002; 89: 704–8)

Letter 1

Sir

This study was designed to show that loop ileostomy is associated with a higher rate of small bowel obstruction (SBO), suggesting (without reference) that 15 per cent of patients with ileostomy suffer this complication. Such high rates of obstruction are seen with ileostomy after ileoanal pouch surgery[1], but not following anterior resection[2,3]. The frequency of stoma-related complications, excluding SBO (colostomy 14, ileostomy 11), does not support the authors' conclusion that colostomy is the preferred stoma. The one patient who required surgery for SBO was found to have obstruction at the ileostomy, but the clinical relevance of this is unclear. Did that patient require laparotomy before the distal anastomosis had healed or was concurrent ileostomy closure performed? Adhesion-related problems may present late and, if loop ileostomies are truly associated with higher rates of SBO, early reporting of trial data may fail to identify this difference. We have seen no further episodes of SBO or other stoma-related complications in the patients reported in 2001 over a median of 60 months' follow-up since stoma closure[4]. In a trial that is similar in method to ours, we wonder whether the higher rate of SBO in this paper by Law *et al.* may be due to their later closure of stomas (ileostomy and colostomy, 180 and 183 days *versus* 62 and 73 days).

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1 Senapati A, Nicholls RJ, Ritchie JK, Tibbs CJ, Hawley PR. Temporary loop ileostomy for restorative proctocolectomy. *Br J Surg* 1993; **80:** 628–30.
2 Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D *et al.* Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. *Lancet* 1999; **353:** 1476–80.
3 Edwards DP, Chisholm EM, Donaldson DR. Closure of loop transverse colostomy and loop ileostomy. *Ann R Coll Surg Engl* 1998; **43:** 112–13.
4 Edwards DP, Leppington-Clarke A, Sexton R, Heald RJ, Moran BJ. Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized clinical trial. *Br J Surg* 2001; **88:** 360–3.

Letter 2

Sir

We have a number of concerns regarding the methodology in this paper. The grade, experience and number of surgeons who performed the total mesorectal excisions and covering stomas are not reported. Selection bias may have occurred, as neither the method of randomization nor patient exclusions are reported explicitly. The authors fail to define clear primary and secondary endpoints. The power calculation is based on a reduction in the incidence of small bowel obstruction. Whilst they define postoperative ileus, no diagnostic criteria are given for small bowel obstruction. The timing of complications and length of follow-up are not reported. How many of these patients required readmission for the reported complications? Detection bias may have occurred as the paper does not record the experience or nature of the observers throughout the study. Statistical conclusions relating to postoperative or stoma-related complications cannot be made as the study is not powered to do so and has not defined any of these outcomes. These methodological weaknesses reduce the weight of the arguments that this paper brings to the current debate on the optimal method of faecal diversion.

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Letter 3

Sir

This study was prospective and body mass index should have been recorded in the two groups since previous studies have shown it to be a risk factor for stomal complications[1]. We were also surprised to note there were no stoma retractions (contrary to the literature rate of 6–17 per cent) in either group[2]. Furthermore, stomal complications such as retraction and prolapse were not defined explicitly. A word of caution is necessary before advocating transverse colostomy for faecal diversion in Western patients. This population has a high body mass index when compared to Asians' and a transverse colostomy may be technically difficult to fashion due to a fatty mesentery and a short residual colon following anterior resection. It is also well known that defunctioning stomas can be associated with major complications[2]. There remains the option of a randomized study comparing stomal diversion *versus* no diversion plus Foley catheter drainage.

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1 Leenen LPH, Kuypers JHC. Some factors influencing the outcome of stoma surgery. *Dis Colon Rectum* 1989; **32:** 500–4.
2 Shellito PC. Complications of abdominal stoma surgery. *Dis Colon Rectum* 1998; **41:** 1562–72.

Authors' reply

Sir

We started to perform total mesorectal excision (TME) in 1993 and three colorectal specialists performed all the operations. Over 200 TME procedures had been performed before the initiation of this trial. Closure of the stoma was also performed in the presence of a specialist, though not necessarily a chief surgeon. Loop ileostomy was our preferred option for proximal diversion before this trial[1,2]; however, small bowel obstruction (SBO) was not uncommon. Our most recent analysis showed that the incidence of SBO following low anterior resection was 13 per cent in patients who had an ileostomy at any stage of their treatment (unpublished data). Gooszen *et al.*[3] also reported small bowel ileus as one of the complications after ileostomy in their randomized trial. Moreover, we noted two patients with late SBO of the 40 who had undergone ileostomy closure[1]. Therefore, SBO was chosen as the main outcome measure in our trial. We finally recommended loop colostomy, mainly because of the lower incidence of SBO; indeed the rates of other stoma-related complications were similar in the two groups. Finally, colostomy closure has been shown to be an easier procedure[4].

We agree with Edwards *et al.* that late closure of a stoma may increase the chance of adhesive SBO. However, all the documented episodes of SBO in the study occurred within 6 weeks of initial surgery. The patient mentioned by Edwards *et al.* underwent reoperation 7 days after initial surgery and the ileostomy was not closed at the same procedure.

The diagnosis of SBO was made using standard clinical features including vomiting, abdominal distension and colicky abdominal pain, as well as radiological features. The objective of this study was to define the early results after stoma closure; the long-term results were not mentioned.

The comment from Arumugam *et al.* about the difference in body mass index between Western and Asian patients is valid. This could account for the difference in our results compared with others[3,4]. Retraction of a stoma is uncommon in our practice. The current low incidence of stoma-related complications has also been demonstrated in a similar study[4].

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1 Poon RT, Law WL, Chu KW, Wong J. Emergency resection and primary anastomosis for left-sided obstructing colorectal carcinoma in the elderly. *Br J Surg* 1998; **85:** 1539–42.
2 Law WL, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. *Am J Surg* 2000; **179:** 92–6.
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Randomized clinical trial of Ligasure^{TM} *versus* open haemorrhoidectomy (*Br J Surg* 2002; 89:154–7)

Sir

Recently several patients have been referred to our unit after Ligasure^{TM} haemorrhoidectomy who have presented up to 1 year following the procedure with soiling, low resting anal pressures and internal anal sphincter defects, suggesting that this operation is not without hazard. Assessment of these patients preoperatively for anal tone and simple questioning concerning function may not be adequate. All new procedures have the potential for anal sphincter damage and their evaluation demands rigorous prospective clinical, manometric and morphological assessment of both the internal and external anal sphincter musculature[1].

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Authors' reply

Sir

We agree with Arumugam[1] that injection sclerotherapy may lead to adherence of the sphincter muscle to the haemorrhoid that could be demonstrated by histological assessment. However the Ligasure™ device does not produce a specimen adequate for histological examination. Importantly, we had no evidence of any functional sphincter deficit at short-term follow-up, and will shortly publish long-term follow-up data that demonstrate no late problems.

Saunders and Abood[2] question the study design. The anaesthetic technique was standard, as were all other aspects of patient care, as one would expect in a randomized clinical trial. Since pain score and analgesic consumption analysis was commenced the day after surgery, and the anaesthetic drugs were short acting, the analgesia on the day of surgery was not relevant. Also, pain score data are more reliable when documented contemporaneously. Therefore standardizing the time when the form would be at hand (i.e. at home) allowed for a more accurate study. We were a little bemused by the statement that 'the inclusion of men and women may have skewed the results' since the randomization provided almost perfect balance between the sexes.

Finally, we are unable to comment on the experience described by Lascelles *et al.* in the light of our apparently trouble-free long-term follow-up. We look forward to reading their paper detailing the complications they have encountered.

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[1] Arumugam PJ. Randomized clinical trial of Ligasure™ *versus* open haemorrhoidectomy *Br J Surg* 2002; **89:** 1068 (Letter).

[2] Saunders SMF, Abood A. Randomized clinical trial of Ligasure™ *versus* open haemorrhoidectomy *Br J Surg* 2002; **89:** 1068 (Letter).

Permanent sacral nerve stimulation for treatment of idiopathic constipation (*Br J Surg* 2002; 89: 882–8)

Sir

The authors conclude that sacral nerve stimulation is an effective treatment for faecal incontinence. Though an interesting and potentially promising technique, one must view these results with a degree of caution. The study group was small and highly selective; all the patients had an intact external anal sphincter and 13 of the 14 patients possessed completely normal pudendal nerve function. Audit of referrals with urge faecal incontinence to our institution revealed that nearly 90 per cent (223 of 252 patients over 7·5 years) had evidence of an external anal sphincter defect and/or prolonged pudendal terminal motor latency. Based on the authors' selection criteria, these patients, who represented the largest clinical group, would have been excluded. In addition, no details were given concerning the number of patients who initially underwent the trial of stimulation but who were deemed unsuitable for permanent stimulation. The authors also appear to dismiss the currently accepted surgical options and suggest that sacral nerve stimulation is the solution for all forms of faecal incontinence. We hold an alternative view that the management of faecal incontinence is complex and a range of current treatments should be adopted, with appropriate patient selection based on careful investigation. Although sacral nerve stimulation represents a novel treatment for faecal incontinence, its benefit in the management of patients with external anal sphincter defect and/or dysfunction secondary to pudendal neuropathy has yet to be established. The conclusions drawn from the study cannot be justified based solely on the treated group.

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Transoesophageal echocardiography shows high risk of gas embolism during laparoscopic hepatic resection under carbon dioxide pneumoperitoneum (*Br J Surg* 2002; 89: 870–6)

Sir

The authors do not provide data to justify their first conclusion that 'the ultrasonically activated scalpel (UAS) causes minimal blood loss during both open and laparoscopic hepatic resection'. The UAS was not compared with finger-fracture or other liver transection techniques, and no other comparative data regarding blood loss during hepatectomy were cited from other relevant published articles. Indeed, the blood loss in their study was greater than that reported by others using finger-fracture[1]. To date, there are no randomized controlled trials to confirm the reduction of blood loss during hepatectomy with the use of the UAS compared with other techniques. While the investigators endeavoured to adjust the central venous pressure (CVP) to correspond with the intraperitoneal pressure of 12 mmHg, the quoted mean CVP at 90 min was less than 12 mmHg. Although episodes of embolism were detected with the CVP above and below the intraperitoneal pressure, it is likely that they occurred more frequently, or were of a larger size, when the venous–intraperitoneal pressure gradient was negative.

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Retrospective study of acute toxicity following short-course preoperative radiotherapy (*Br J Surg* 2002; 89: 889–95)

Sir

It is still unclear whether patients with tumour node metastasis stage IV rectal cancer benefit from preoperative radiotherapy. There is no evidence to suggest that these patients 'could be spared potential toxicity of short-course preoperative radiotherapy'. In the cited Dutch total mesorectal excision trial[1], preoperative radiotherapy had no effect on local recurrence in patients with stage I and IV disease in a univariate analysis, but in multivariate analysis no significant interaction was found between the tumour node metastasis subgroups analysed and treatment effect. In fact, patients with distant disease who received preoperative radiotherapy in the Dutch trial had a 10·1 per cent local recurrence rate at 2 years *versus* 23·8 per cent for patients who had no preoperative radiotherapy. Lack of statistical significance of this difference was related more to small sample size than to ineffectiveness of the preoperative radiotherapy. The randomized controlled trials to date[1–3] do not provide definitive conclusions about the use of preoperative radiotherapy in patients with metastatic disease, mainly because such patients are not enrolled in trials if identified preoperatively. However, there are at least two subgroups of patients with distant disease who, in our opinion, will benefit from preoperative radiotherapy: first, patients with resectable distant disease and, second, those in whom control of metastases can be achieved with local ablative techniques. As these patients are treated for potential cure there are no arguments to 'spare' them from preoperative radiotherapy, so the decision to not irradiate patients with stage IV disease before surgery should be considered carefully.

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1 Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.
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Proposal for limited surgery for gastric cancer

Sir

In line with the advocacy in recent years of limited surgery to preserve function, minimal resection, as well as minimization of the area of lymph node dissection, is indicated in the guidelines for treatment of early-stage gastric cancer[1]. Although operations such as partial resection and pylorus-preserving gastrectomy have been used for many years, they have only recently been shown to be rational procedures that do not involve a reduction in potential curability. Thus, long-term results of such procedures are not yet known. These methods are listed in the guidelines as 'experimental-stage' treatments. It is stated that efforts must be made to improve the accuracy of preoperative diagnosis so as to reduce the discrepancies between preoperative macroscopic diagnosis and postoperative pathological diagnosis.

Before performing limited surgery for early-stage gastric cancer, informed consent must be obtained from the patient following full explanation of the possibility of inaccuracies both in preoperative diagnosis of the depth of penetration and in preoperative and intraoperative diagnoses of lymph node metastasis. Furthermore, there is the possibility of alteration in the procedure during the operation and/or re-operation if lymph node metastasis is detected. The propriety of limited surgery needs to be determined by evaluation of treatment results in a large population of patients who have given informed consent and who have been selected as candidates for such surgery on the basis of rational criteria determined from the results of past cases.

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Oxford Textbook of Surgery on CD-ROM, Single User Version. 2nd ed.

P. J. Morris and W. C. Wood (eds)
Illustrated 2002. Oxford Oxford University Press £250 00

The first edition of this book became my standard source of surgical reference. I bought the second edition when it was published in 2000 and it was three volumes comprising 3602 pages. Most of the contributors to the first edition were working, or had worked, in Oxford, UK or Boston, USA. The second edition is very comprehensive and more cosmopolitan, having more than 300 authors from North America and Europe. Although its content is aimed primarily at the general surgeon, it contains appropriate coverage of the major topics in other specialties such as cardiac, orthopaedic and paediatric surgery. Frequently, individual topics within the 51 sections provide differing approaches reflecting practice in the authors' countries. All the previously published sections have been rewritten and, in particular, the role of minimally invasive surgery within each field has been addressed. New sections, such as nutrition and shock, have been added. It is lavishly illustrated with colour photographs, radiographs, line drawings and tables. There is hardly a working week that I do not open it.

It has now been produced in CD-ROM format. To read the CD-ROM and, in particular, to reproduce the excellent illustrations requires a high-resolution colour monitor and either Windows® 95, 98, Me, NT 4·0, 2000 or XP. The software is browser based. I am not particularly computer literate, but after a few minutes I became reasonably adept at navigating the contents. To avoid breaking up the text on a small screen, illustrations are hidden by default but are easily accessed with the mouse. I still prefer reading books; however, unlike previous computerized versions of many textbooks, this CD-ROM is user-friendly and it takes up less space on the bookshelf. It can also be installed on to a hard drive, allowing faster access, but this requires 150 MB of memory.

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Pocket Companion to Sabiston Textbook of Surgery. 16th ed.

C. M. Townsend Jr. (ed.)
215 × 125 mm Pp 899 Illustrated 2002 London. WB Saunders. £25 95.

This publication offers a portable form of a comprehensive and successful textbook, now in its sixteenth edition, compiled by distinguished editors and featuring field leaders as chapter authors. The text covers the generality and major specialties of surgery and many of the subspecialties of general surgery. Presented as bulleted text rather than formal prose, the authors try to present the salient and pertinent points of each disease entity. The quality of the reduction varies from chapter to chapter with disproportionate weight given to some aspects at the expense of other, perhaps more important or common, conditions; for instance, one questions the need for, and economy of, exhaustive tables detailing the properties of anaesthetic inhalation agents. Used in conjunction with the parent volume, this companion serves a function as an *aide-mémoire*, but it will be of only limited use to a reader approaching a topic for the first time. Finally, this book fits in only half the pockets of the white coats of the doctors polled in our office and, given the crowded marketplace, it faces fierce competition.

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Scientific Surgery

Rigg JRA, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW *et al.* for the MASTER Anaesthesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. *Lancet* 2002; **359:** 1276–82.

Some 915 high-risk patients were studied. Use of an epidural reduced postoperative pain scores for the first 3 days and reduced the rate of respiratory failure; however, overall mortality in both groups was similar.

Lewis RT. Oral *versus* systemic antibiotic prophylaxis in elective colon surgery: a randomized study and meta-analysis send a message from the 1990s. *Can J Surg* 2002; **45:** 173–80.

Some 215 patients were randomly allocated oral neomycin and metronidazole, in addition to parenteral antibiotic prophylaxis. The combination regimen reduced the wound infection rate (five *versus* 17, risk ratio 0·27, 95 per cent confidence interval 0·11 to 0·75, $P < 0{\cdot}01$). The meta-analysis of 13 randomized trials confirmed the superiority of combination prophylaxis.

Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A *et al.* for the ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; **346:** 975–80.

A total of 332 patients were included and randomly allocated 21 days extra thromboprophylaxis after the initial 6–10 days. At 1 month the deep venous thrombosis rate on venography was 12 per cent for placebo and 4·8 per cent for extra enoxaparin ($P = 0{\cdot}02$). This difference persisted after 3 months.

Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomized trials. *Lancet* 2002; **359:** 909–19.

This review included 250 000 women who had been followed for a median of 15 years. Screening produced a 21 per cent reduction in breast cancer deaths, the greatest reduction being in the 60–69-year-old age group. The advantages of screening persisted in the long term.

Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002; **35:** 413–21.

In this trial that included 831 patients, warfarin in addition to aspirin reduced the mortality rate (23 *versus* 31·8 per cent, $P = 0{\cdot}0001$), but only improved graft patency in patients with small-calibre (6 mm) prosthetic bypass grafts (57·9 *versus* 71·4 per cent, $P = 0{\cdot}02$).

Lens MB, Dawes M, Goodacre T, Newton-Bishop JA. Elective lymph node dissection in patients with melanoma. Systematic review and meta-analysis of randomized controlled trials. *Arch Surg* 2002; **137:** 458–61.

The review included 1533 procedures from three trials that compared elective and delayed lymphadenectomy in patients with no palpable nodes. The pooled odds ratio for reduction in mortality in the trials was 0·86 (95 per cent confidence interval 0·68 to 1·09) and was not statistically significant.

Strandness DE, Dalman RL, Panian S, Rendell MS, Comp PC, Zhang P *et al.* Effect of cilostazol in patients with intermittent claudication: a randomized double-blind, placebo-controlled study. *Vasc Endovasc Surg* 2002; **36:** 83–91.

Two different doses of cilostazol taken for 24 weeks were compared with placebo in 394 subjects. Maximum walking distance was improved by 21 per cent by 100 mg twice daily ($P = 0{\cdot}0003$) and 7 per cent by 50 mg twice daily (P not significant).

Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H *et al.* Endovenous obliteration *versus* conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. *J Vasc Surg* 2002; **35:** 958–65.

This study that included only 28 patients showed that VNUS (VNUS Medical Technologies, San Jose, California, USA) caused less post-operative pain and shorter convalescence than conventional surgery, although clinical results were similar. Costs were greater for VNUS.

Frantzides CT, Madan AK, Carlson MA, Stavropoulos GP. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair *versus* simple cruroplasty for large hiatal hernia. *Arch Surg* 2002; **137:** 649–52.

The addition of a polytetrafluoroethylene patch for crural repair reduced hernia recurrence rates from eight (22 per cent) to nil in this trial that included 72 operations.

Heah SM, Seow-Choen F, Eu KW, Ho YH, Tang CL. Prospective, randomized trial comparing sigmoid *versus* descending colonic J-pouch after total rectal excision. *Dis Colon Rectum* 2002; **45:** 322–8.

The study included 92 consecutive patients, with a median follow-up of 12 months. There were no significant differences in pouch function or anorectal physiology parameters between the two pouch constructions.

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The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; **354**: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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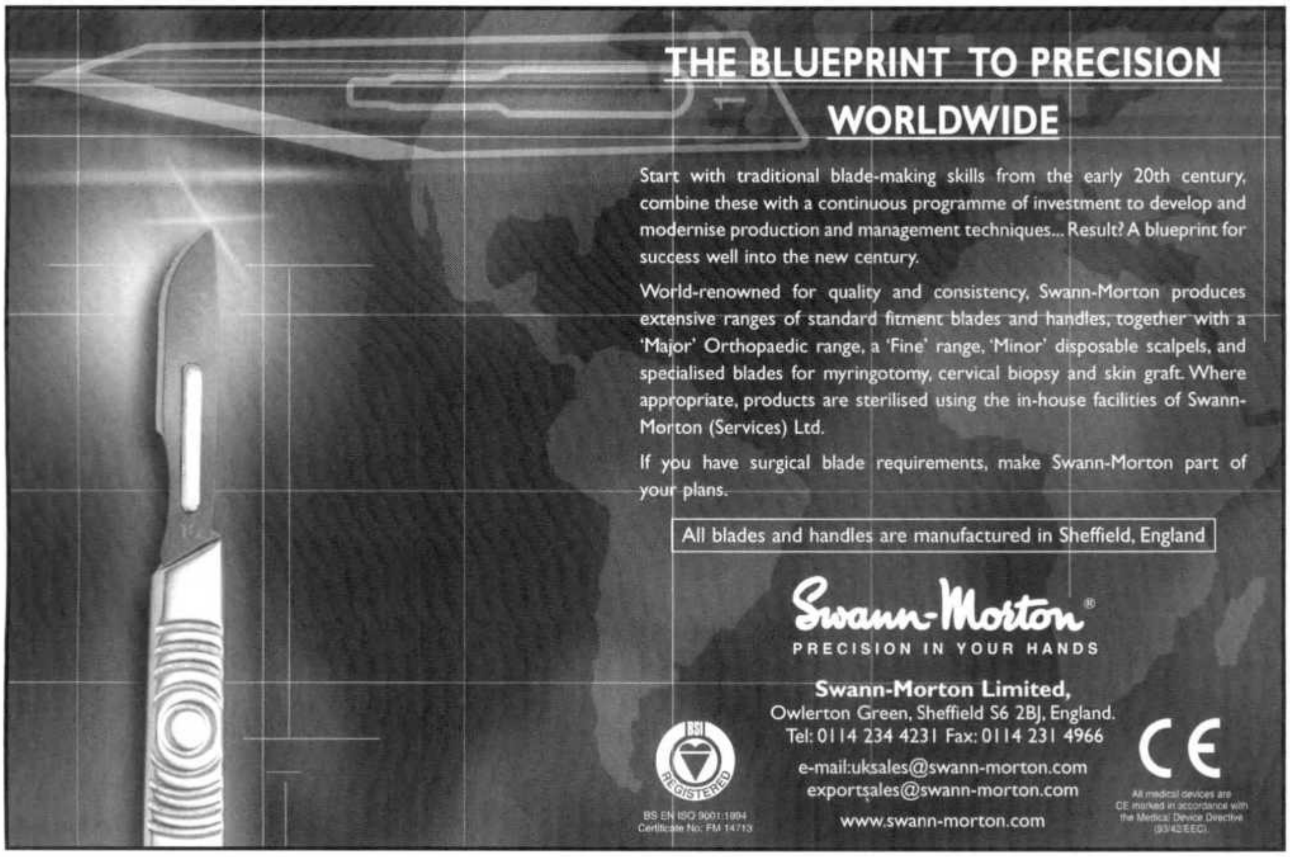

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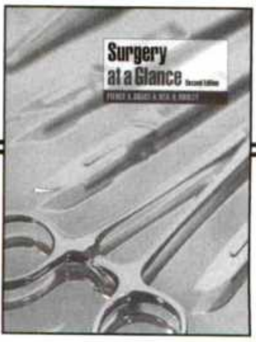

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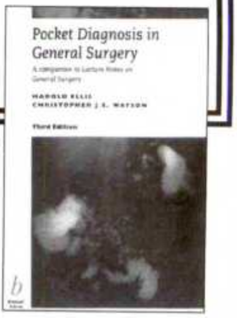

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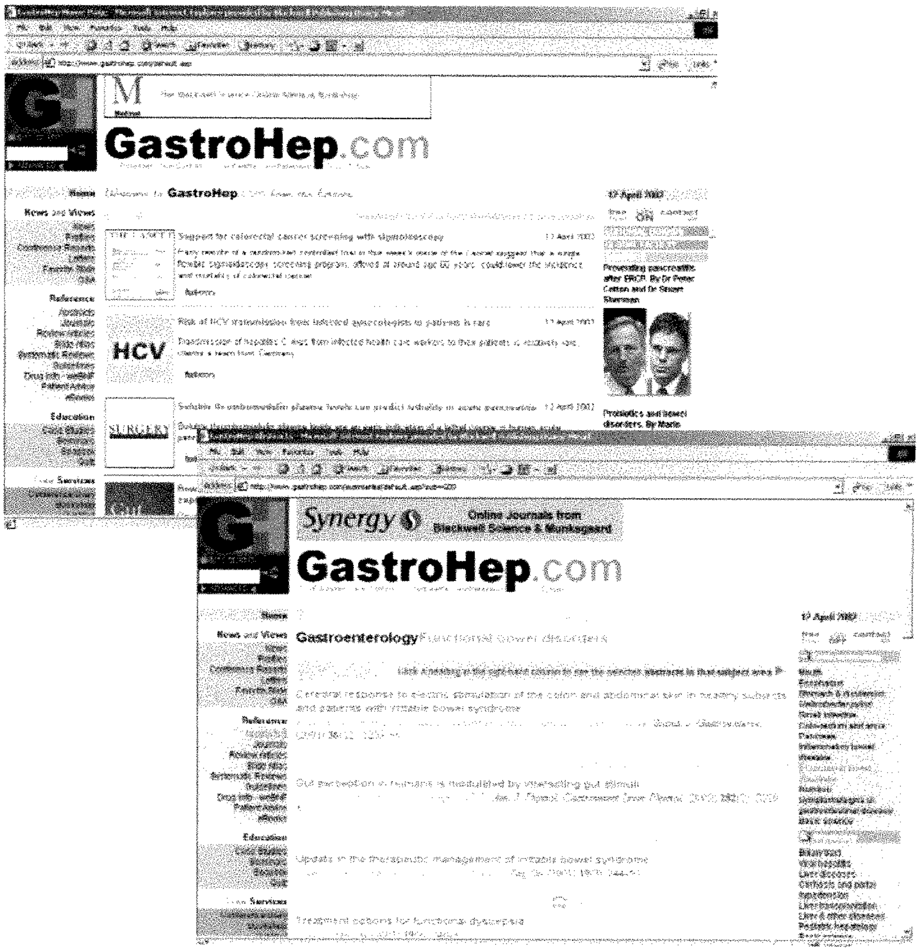
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Leading article

Advances in endocrine therapy of metastatic breast cancer

W. J. Gradishar and M. Morrow

The Feinberg School of Medicine, Northwestern University, 676 North St Clair Street, Chicago, Illinois 60611, USA
(e-mail: w-gradishar@northwestern.edu)

Endocrine therapy has been an effective strategy for patients with advanced breast cancer for over a century and the options available to patients with hormone sensitive, advanced breast cancer have continued to expand. The new therapies that are briefly reviewed below have been developed as a result of advances in medicinal chemistry and a better understanding of steroid hormone receptor biology.

Aromatase inhibitors

The aromatase enzyme is critically responsible for the conversion of androgen precursors into oestrogen. The rationale for using aromatase inhibitors is to decrease the levels of both circulating oestrogen and intratumoral oestrogen by inhibiting the conversion of androstenedione into oestrogen. In premenopausal women, the primary site of aromatase activity, and as a result oestrogen synthesis, is the ovary. While aromatase inhibitors are ineffective in suppressing such premenopausal ovarian aromatase activity, in postmenopausal women they are effective in suppressing extraovarian sites of aromatase enzyme activity (i.e. adipose tissue, muscle, liver, etc.). In addition, human breast tumours are themselves known to have aromatase activity.

Older aromatase inhibitors, such as aminoglutethimide, were able to suppress aromatase activity by more than 90 per cent. However, aminoglutethimide was non-selective and interfered with other enzymes in the cortisol and aldosterone pathways. As a result, it was associated with toxicities that were only partially alleviated by the administration of concurrent steroids. The new aromatase inhibitors, both steroidal (exemestane) and non-steroidal (anastrozole, letrozole), are more potent and selective than their predecessors.

Until recently, the second-line endocrine therapy of choice following tamoxifen was progestins. In pivotal randomized clinical trials, involving more than 2200 postmenopausal patients, the new aromatase inhibitors were compared with megestrol acetate. The aromatase inhibitors were at least as effective, if not superior to, megestrol acetate in each of the trials; three trials are shown in *Table 1*[1–3]. The new aromatase inhibitors were also better tolerated by patients than megestrol acetate, and could be administered as a single tablet per day. As a result of these clinical trials, the new selective aromatase inhibitors have become the preferred endocrine therapy following treatment with tamoxifen.

More recently, data have become available from clinical trials (*Table 2*) in which women with oestrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive, or ER/PR-unknown tumours and an adjuvant tamoxifen-free interval of between 6 and 12 months, were randomized at relapse to tamoxifen or a selective aromatase inhibitor (anastrozole, letrozole or exemestane). The pooled data from the two randomized clinical trials comparing anastrozole with tamoxifen (1021 patients) show that anastrozole is at least as effective as tamoxifen in the first-line setting[4,5]. Both therapies were well tolerated but, interestingly, thromboembolic disease was more common in patients randomized to tamoxifen. The patient eligibility criteria for the pivotal clinical trial comparing letrozole with tamoxifen (907 patients)[6] were identical to those of the anastrozole trials. Analysis of efficacy endpoints in this trial showed that patients treated with letrozole had a statistically significant superior objective response rate, clinical benefit rate and

Table 1 Aromatase inhibitors *versus* megestrol acetate

	Exemestane 25 mg *versus* MA[1]	Anastrozole 1 mg *versus* MA (pooled data)[2]	Letrozole 2·5 mg *versus* MA[3]
No. of patients	366 *versus* 403	263 *versus* 253	174 *versus* 189
CR + PR (%)	15·0 *versus* 12·4	12·4 *versus* 12·2	23·6 *versus* 16·4*
Median TTP (months)	4·7 *versus* 3·8*	4·8 *versus* 4·6	5·6 *versus* 5·5
Median survival (months)	NR *versus* 28·4*	26·7 *versus* 22·7*	25·3 *versus* 21·5

MA, megestrol acetate; CR, complete response; PR, partial response; TTP, time to progression; NR, no response. *Statistically significant

Table 2 Aromatase inhibitors *versus* tamoxifen for advanced breast cancer

Trial	Tamoxifen	Aromatase inhibitor	*P*
Europe, Australia, South America[4]			
ER + and/or PR + or unknown			
Treatment	20 mg	Anastrozole 1 mg	
No. of patients	328	340	
Response rate (%)	33	33	n.s.
Clinical benefit (%)*	56	56	n.s.
Time to progression (months)	8·3	8·2	n.s.
North America[5]			
ER + and/or PR + or unknown			
Treatment	20 mg	Anastrozole 1 mg	
No. of patients	182	171	
Response rate (%)	17	21	n.s.
Clinical benefit (%)*	46	59	0·01
Time to progression (months)	5·6	11·1	0·005
Mouridsen *et al.*[6]			
ER + and/or PR + or unknown			
Treatment	20 mg	Letrozole 2·5 mg	
No. of patients	454	453	
Response rate (%)	21	32	0·002
Clinical benefit (%)*	38	50	0·004
Time to progression (months)	6·0	9·4	0·001
Overall survival (months)	30	34	0·5
EORTC[8]			
ER + and/or PR +			
Treatment	20 mg	Exemestane 25 mg	
No. of patients	56	56	
Response rate (%)	14	44	< 0·05
Clinical benefit (%)*	39	55	n.s.
Time to progression (months)	5·2	8·9	n.s.

*Clinical benefit = complete response + partial response + stable disease for 24 weeks or more. ER +, oestrogen receptor positive; PR +, progesterone receptor positive; EORTC, European Organization for Research and Treatment on Cancer; n.s., not significant

time to disease progression. In addition, overall survival at 1 and 2 years was better for patients treated with letrozole. There are only limited data from a comparison of exemestane with tamoxifen (112 patients) in the first-line setting, but a preliminary analysis suggests that response rate and time to disease progression are superior for patients treated with exemestane[8]. The mature data from the anastrozole and letrozole trials clearly support these agents as alternatives, if not superior alternatives, to tamoxifen as first-line therapy for postmenopausal patients with ER- and/or PR-positive metastatic breast cancer.

The efficacy of the aromatase inhibitors as treatment for advanced disease has prompted intense interest in their potential role as adjuvant therapy for early-stage breast cancer in postmenopausal women. The early results of the Arimidex, Tamoxifen, Alone or in Combination trial comparing anastrozole, tamoxifen and the combination of anastrozole plus tamoxifen show an improved disease-free survival for patients treated with anastrozole compared with tamoxifen or the combination. In addition, patients treated with anastrozole had fewer contralateral breast cancers than those in the other two treatment groups. Although hot flushes and vaginal complaints were less common in patients treated with anastrozole, the fracture rate was higher. Longer follow-up of this trial will be critical in the assessment of the true impact of anastrozole in this patient population. Several other large, randomized clinical trials are being conducted around the world to evaluate the impact of letrozole and exemestane in the adjuvant setting.

Fulvestrant

The first large clinical trials evaluating the new selective ER downregulator, fulvestrant (Faslodex; AstraZeneca, Macclesfield, UK), were reported recently[9,10]. Fulvestrant in both preclinical and clinical trials has been shown to have properties distinct from those of tamoxifen and its analogues. Fulvestrant has a steroidal structure similar to that of the naturally occurring hormone oestradiol, differing only in the addition of a long side chain. The mechanism of action of fulvestrant differs from that of tamoxifen. Most importantly, the fulvestrant–ER complex is degraded

Table 3 Fulvestrant *versus* anastrozole for postmenopausal stage IV breast cancer

	North America[9]		Europe[10]	
	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
No. of patients	206	194	222	229
Median TTP	5·4 months	3·4 months	167 days	156 days
RR (%)	18	18	21	16
CB (CR + PR + SD) (%)	42	36	45	45

TTP, time to progression; RR, response rate; CB, clinical benefit; CR, complete response; PR, partial response; SD, stable disease

rapidly, resulting in loss of ER protein. The net effect of fulvestrant is decreased transcription and ER-dependent cell division. Fulvestrant is administered as an intramuscular injection.

Promising results from a small phase II trial of fulvestrant in patients with tamoxifen-refractory disease provided the rationale for the development of randomized clinical trials comparing fulvestrant with anastrozole in postmenopausal women whose disease had progressed on or after tamoxifen therapy. One trial was conducted in North America[9] and the other in Europe, South America and Australia[10]. A total of 851 patients was recruited to these two trials. The important endpoints of these studies are outlined in *Table 3*. The results of these two large randomized trials establish fulvestrant as a novel endocrine therapy with a unique mechanism of action that has tumour activity equivalent to that of anastrozole in patients who have already received treatment with tamoxifen. Data are now maturing from a completed clinical trial comparing fulvestrant with tamoxifen as first-line endocrine therapy for patients with metastatic breast cancer.

Conclusions

Continued progress in the development of new endocrine therapies for breast cancer has expanded treatment options for patients. Ongoing clinical research will address the issue of optimal sequencing of these agents in the metastatic disease setting, and their role in patients with early-stage breast cancer and healthy women at high risk of developing breast cancer.

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BJS Research Bursary Winners 2002

There were 55 applications for a *BJS* Research Bursary this year and for the first time two of the awards have been given to surgeons from outside the United Kingdom. The *BJS* Council is delighted to offer awards of £10,000 to the following three surgeons and their teams:

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Bristol Royal infirmary, Bristol, UK
The calcium receptor and the potential for bone metastasis in breast cancer

Dr M. Poeze MD
University Hospital Maastricht, Maastricht, The Netherlands.
Effect of modulation of nitric oxide metabolism during surgical sepsis

Professor E. Garcia-Granero MD
University Hospital, Valencia, Spain
The use of tonometry to evaluate the effects of administration of supplemental oxygen on colorectal anastomosis

Further details including a list of highly commended entries can be found on the *BJS* website (www.bjs.co.uk).

Jonothan J. Earnshaw
Editor

Leading article

Iatrogenic impotence and rectal dissection

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Colorectal surgeons are becoming ever more aware of the details of the surgical anatomy of the rectum and surrounding pelvic structures in the drive to improve not only the oncological but also the functional outcome of pelvic surgery. In the past, impotence after proctectomy has been overattributed to non-surgical factors, such as the presence of a stoma or the fear of recurrent cancer. Higher impotence rates in ileostomists have never been demonstrated[1] and there is now increasing recognition of the role of parasympathetic nerve injury.

Traditionally, subjective assessment methods (interview or questionnaire) have been used to explore impotence after proctectomy, but recent objective evaluation has proved illuminating. Nocturnal penile tumescence monitoring, assuming that nocturnal erections during rapid eye movement sleep are equivalent to sexually induced erections, strongly supports the aetiological role of parasympathetic nerve injury. Patients with impotence after proctectomy for rectal cancer or inflammatory bowel disease have a significantly reduced number of tumescent events when monitored for two nights, compared with matched potent controls[2]. Intriguingly, the phosphodiesterase type 5 inhibitor sildenafil (Viagra; Pfizer, Tadworth, UK) helps impotent patients with diminished nocturnal tumescent activity (and thus parasympathetic nerve damage) more than those with preserved activity[2]. Sildenafil works by augmenting the vasodilator effect of parasympathetic neural tone on the choke arterioles governing inflow to the erectile cavernous chambers of the penis. It requires the presence of at least some intact and functioning parasympathetic nerve fibres to exert its effect[3], and is generally less effective when profound neural injury underlies impotence[4]. This finding supports the role of parasympathetic nerve injury and, in particular, suggests that the neural lesion in postproctectomy impotence is frequently partial.

Where does this nerve injury take place? It is difficult to be certain about where most injuries occur, but there are four key zones of risk of autonomic nerve damage. The risk of sympathetic nerve damage occurs in the abdomen during ligation of the inferior mesenteric artery pedicle, and high in the pelvis during initial posterior rectal dissection adjacent to the large hypogastric nerves. Lower down, risk to the parasympathetic nerves occurs while dissecting laterally near the pelvic plexus, and during deep dissection of the anterior aspect of the rectum away from the seminal vesicles and prostate near the cavernous nerves.

Accumulating evidence suggests that most trauma to parasympathetic nerves occurs during deep anterior dissection. First, published impotency rates after abdominoperineal excision are consistently higher than after anterior resection for rectal cancer, reflecting a deeper rectal dissection[5]. Second, operations for rectal cancer that involve rather than spare the anterior rectal quadrant are associated with a higher rate of impotence[6]. Third, impotency rates after close rectal *versus* mesorectal excision for inflammatory bowel disease are the same when a close rectal dissection is used immediately behind the prostate in an otherwise mesorectal technique[7]; this suggests the importance of the anterior dissection. Finally, in the Singapore trial of laparoscopically assisted *versus* open surgery for rectal cancer, published in this edition of *BJS*[8], impotency rates were tenfold higher after laparoscopically assisted surgery, yet ejaculatory and bladder dysfunction were equivalent in the two groups. This indicates that nerve injury takes place distal to the origin of nerves supplying motor function to the bladder, distal to the pelvic plexus, i.e. injury affects the cavernous nerves during anterior dissection (which is generally the most technically difficult point to obtain good retraction and vision during laparoscopic deep pelvic dissection in men).

In the authors' opinion, injury to the pelvic plexus is uncommon unless it is tented up during ligation of the so-called 'lateral ligaments', a technique on the wane with declining belief in this anatomical concept[9]. Urological studies have established the anterior cavernous nerves as central to the development of erectile dysfunction after pelvic surgery[10]. These small nerves are extremely close during anterior dissection, yet are not visualized. They arise as branches from two discrete neurovascular bundles that sit just anterior to the lateral borders of Denonvilliers' fascia between the rectum and the prostate and seminal vesicles. Anterior dissection deep in the pelvis can be especially difficult, particularly in a male with a bulky tumour, and occasionally troublesome bleeding requires diathermy control. The mesorectal plane is also slightly less well defined anteriorly than posteriorly. It is not difficult to imagine how these small nerves may be damaged.

It seems important to define the principal zone of injury so that suitable steps may be taken to prevent postproctectomy impotence. The choice of surgical plane for anterior rectal dissection is a factor within the surgeon's control; it has an influence on impotence and should be better defined. A consensus has been reached regarding the anatomy of the planes of posterior and lateral rectal dissection (mesorectal plane), but this is not the case anteriorly. What planes are available anteriorly; can the surgeon easily differentiate them; and which should be used and when? There are three planes, and dissection within them involves resection of none, some, or all of the structures lying between the anterior rectal wall and the prostate and seminal vesicles. The planes are, respectively, characterized by the anterior mesorectum, the fascia propria of the rectum, and Denonvilliers' fascia.

The close rectal dissection plane, immediately on the rectal musculature within the mesorectal fat, is not a natural anatomical plane. Some will favour this dissection for inflammatory bowel disease, but it is technically difficult and is probably required only behind the prostate to minimize impotence[7]. The mesorectal plane, immediately outside the fascia propria, is an anatomical plane that should be familiar to the colorectal surgeon; it is the standard plane used in operations for rectal cancer. Dissection in this plane separates the fascia propria of the rectum from Denonvilliers' fascia, which is left intact on the prostate and seminal vesicles and not the anterior surface of the rectum[11]. An anterior mesorectal dissection remains posterior to Denonvilliers' fascia with the cavernous bundles relatively protected by it. Use of the extramesorectal plane, exposing and staying immediately on the prostate and seminal vesicles, results in a resection of Denonvilliers' fascia which can be identified on the anterior surface of the extraperitoneal rectum[11]. As dissection is conducted in the plane anterior to Denonvilliers' fascia, the risk of damage to the cavernous nerves is theoretically highest. While some surgeons recommend the routine use of this plane, in the authors' opinion it should be used only when the risk of leaving a tumour-positive anterior resection margin is high (when the tumour threatens the anterior circumferential margin).

Sexual dysfunction in women after rectal surgery has not received much attention, and the surgical anatomy of the autonomic nerves and corresponding autonomic nerve lesions are poorly understood. This area presents considerable opportunities for further research. In men the plane of anterior rectal dissection is now known to be critical with respect to sexual function; it should be defined relative to Denonvilliers' fascia and the anterior mesorectum. Maximum preservation of the cavernous nerves, when possible, is especially important as a result of the advent of modern pharmacological agents for impotence that act by amplifying otherwise suboptimal function in these nerves[12].

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Review

Comparison of endoscopic sphincterotomy and laparoscopic exploration of the common bile duct

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Background: Laparoscopic exploration of the common bile duct is becoming more popular, although endoscopic sphincterotomy remains the usual treatment for bile duct stones. However, loss of the biliary sphincter causes permanent duodenobiliary reflux, and recurrent stone disease and biliary neoplasia may be a consequence.

Methods: A systematic literature review was conducted to compare laparoscopic exploration with endoscopic sphincterotomy. A text word search of the Medline, Pubmed and Cochrane databases, and a manual search of the citations from these references, was used.

Results: Endoscopic sphincterotomy is associated with a median (range) mortality rate of 1 (0–6) per cent, compared with 1 (0–5) per cent for laparoscopic bile duct exploration. The median (range) rate of pancreatitis following endoscopic sphincterotomy is 3 (1–19) per cent; this is a rare complication after laparoscopic duct exploration. The combined morbidity rate for laparoscopic cholecystectomy and endoscopic sphincterotomy is 13 (3–16) per cent, which is greater than 8 (2–17) per cent for laparoscopic bile duct exploration. Randomized trials are few and contain relatively small numbers of patients. They show little overall difference in rates of duct clearance, but a higher mortality rate and number of hospital admissions are noted for endoscopic sphincterotomy compared with laparoscopic bile duct exploration. Endoscopic sphincterotomy is associated with recurrent stone formation (up to 16 per cent) with associated cholangitis. It is also associated with bacterobilia and chronic mucosal inflammation. The late development of bile duct cancer has been reported in up to 2 per cent of patients.

Conclusion: Laparoscopic exploration of the common bile duct may be a better way of removing stones than endoscopic sphincterotomy plus laparoscopic cholecystectomy.

Paper accepted 13 August 2002

British Journal of Surgery 2002, 89, 1495–1504

Introduction

The advent of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy has dramatically changed the management of bile duct stones. Mortality in elderly patients fell from reported rates of up to 7·4 per cent for open bile duct exploration to 0·2–2·3 per cent[1,2]. The value of endoscopic sphincterotomy was particularly obvious in those who were unfit for general anaesthesia, in whom it was, and still is, accepted that bile duct stones may be removed with the gallbladder left *in situ*[3–5]. Since its inception, ERCP with sphincterotomy has been used increasingly in elderly patients with bile duct stones and serious co-morbidity, who would otherwise have posed a therapeutic problem – often insuperable. Conversely, young healthy patients were still treated by open operation without much mortality[6] and with preservation of the biliary sphincter.

The second revolution in the management of bile duct stones came with the development of laparoscopic cholecystectomy[7,8]. Suddenly, gallbladder stones could be treated surgically without laparotomy. By this time, however, endoscopic sphincterotomy was in widespread use, and many surgeons favoured this endoscopic method of treating bile duct stones rather than continuing with open operation. An added advantage is that endoscopic sphincterotomy can be performed before or after laparoscopic cholecystectomy, depending on the circumstances. Consequently, a group of young and fit patients, previously treated by bile duct exploration at open operation following a positive finding on operative cholangiography, could now undergo sphincterotomy.

ERCP with sphincterotomy is quick and often painless; it is usually successful. However, there are reports of adverse effects of endoscopic sphincterotomy in the short, medium and long terms. These include pancreatitis, duodenal perforation and bleeding, and failure to clear the duct in the short term. In the medium term cholangitis and recurrent stone formation may occur, and in the longer term bile duct malignancy. Recently, laparoscopic exploration of the common bile duct has been described, with apparently good results[9,10]. The aim of this review of the available literature was to try to determine the appropriate management of bile duct stones.

Methods

An electronic search of the Medline and Pubmed databases and the Cochrane Controlled Trials Register was conducted using the following keywords: common bile duct stones, common bile duct calculi, endoscopic cholangiopancreatography, ERCP, endoscopic sphincterotomy, ES, laparoscopic cholecystectomy, cholecystectomy, laparoscopic common bile duct exploration, common bile duct exploration. These terms were mapped to Medline Subject Headings (MESH) terms as well as being searched for as text items. The titles and abstracts of 'hits' were assessed and the relevant articles were acquired. The references cited in retrieved articles and review articles were cross-checked manually to locate other relevant papers. Studies in all languages were considered. The relevance and validity of each article was assessed and included if it reported a series of 50 or more patients. All randomized trials were included, irrespective of sample size. Papers published before 1990 and those with fewer than 50 patients were excluded because of a desire to include only those studies for which reasonable experience in either technique could be assumed, in order to minimize any effect of technical inexperience. The end-points of the study were short-term efficacy, mortality, complications, and long-term results.

Results

Published data on endoscopic sphincterotomy are shown in *Tables 1* and *2a*. The reported success rates for sphincterotomy vary from 79 to 98 (median 92) per cent and duct clearance from 75 to 96 (median 91) per cent respectively. These rates do not improve in larger or more recent studies. Total complication rates vary from 2 to 24 (median 8) per cent and mortality rates from 0 to 6 (median 1) per cent. Pancreatitis occurs after diagnostic ERCP and this complication is increased after sphincterotomy. Reported incidences following sphincterotomy vary from 1 to 19 (median 3) per cent, but associated deaths are not usually reported separately. The data of Deans *et al.*[17] appear to show that age has no influence, but patients aged less than 55 years were six times more likely to suffer this potentially serious complication than older patients. Tham *et al.*[29] and Freeman *et al.*[13] recorded a similar but less marked bias towards increased risk in younger patients. Cholangitis occurs in up to 4 per cent of patients, and haemorrhage has an overall incidence of 1–6 per cent, with a mortality rate of about 2 per cent. Duodenal perforation occurs in 1–2 per cent, also resulting in a high mortality rate. The overall mortality rate following endoscopic sphincterotomy is 0–6 per cent. There has been little change in the rate of complications over the decades; indeed the rate of postprocedure pancreatitis appears to have risen, from a median (range) of 1 (1–4) per cent in the 1980s to 3 (1–19) per cent in the 1990s.

Medium-term results are now increasingly available, and are summarized in *Table 3*. The rate of late biliary symptoms varies from 7 to 11 per cent. Reported complications consist mainly of recurrent stones (2–16 per cent) with or without sphincterotomy stenosis (1–7 per cent) and cholangitis (1–6 per cent). The recurrent stone rate increases according to the length of follow-up. These tabulated studies have a median follow-up of 8 (range 1–15) years from the initial sphincterotomy. Ikeda *et al.*[42] reported a recurrent stone rate of 6 per cent after a mean of 2·4 years, even though the mean follow-up period in this study was only 3·7 years. Recent data from Japan show a continuing accrual of recurrent stones up to 25 years after sphincterotomy, with no sign of a plateau[37]. *Table 4* summarizes reports in the literature describing further long-term sequelae of sphincterotomy or biliary bypass procedures. Bacterobilia, mucosal hyperplasia and bile duct cancer have been recorded, including two reports of cancer after endoscopic sphincterotomy[26,37].

Laparoscopic common bile duct exploration was started in the early 1990s and several reports are available. These are summarized *Tables 2b* and *5*. Some describe the early and later experience of the same authors; all have been included. Bile duct clearance rates are over 90 per cent in 70 per cent of reports, with a median retained stone rate of 5 (range 0–19) per cent and a median rate of conversion to open operation of 4 (range 1–20) per cent. The median mortality rate is 1 (range 0–5) per cent and the complication rate 8 (range 2–17) per cent. The success, mortality and morbidity rates show no improvement with the number of patients in the series.

The results of randomized trials comparing ductal exploration with endoscopic sphincterotomy and subsequent laparoscopic cholecystectomy are shown in *Table 2a,b*. When these studies alone are summated, the rates of duct clearance and length of stay are similar for both

Table 1 Success rates and early complications of endoscopic sphincterotomy

Reference	Year	No. of patients	CBD stones (%)	Age (years)	Successful sphincterotomy (%)	Successful duct clearance (%)	Morbidity (%)	Pancreatitis (%)	Haemorrhage (%)	Cholangitis (%)	Duodenal perforation (%)	Mortality (%)
Siefert *et al.*[11]	1982	9041 (25 centres)	84				8	1	2	1	1	
Safrany *et al.*[12]	1978	3853 (15 centres)	85		93*	90	7	1	2	1	1	1
Freeman *et al.*[13]	1996	2347	68				8	5				2
Geenan *et al.*[14]	1981	1250 (21 centres)	88				9	3	2	2	1	
Sherman *et al.*[15]	1991	1204	97	55*			5					1
Vaira *et al.*[16]	1989	1000				87	7					1
Deans *et al.*[17]	1997	958		73*			2	1				0
Lambert *et al.*[18]	1991	602		76†	91		10	3	5	2	1	2
Wojtun *et al*[19]	1997	483	100		96		7	3	2	1	1	
Escourrou *et al.*[20]	1984	443	100		92	96	7	1	4		1	
Leese *et al.*[21]	1985	394	81	67*	98	92	10	3	6	2	1	1
Welbourn *et al.*[22]	1995	306	53	50*	79							
Viceconte *et al.*[23]	1981	296	86	62*	86	82	7		5	2		1
Siegel[24]	1981	267	87	66*	98		6	1	3	1	1	1
Boender *et al.*[25]	1994	242	100	70*	94	82	14	2	6	4	2	
Prat *et al.*[26]	1996	169	100	< 70*		90	6		1	3	1	
Sugiyama and Atomi[27]	1998	115	100	50 (< 60)†	97	96	8	4	3	1	1	
Bergman *et al.*[28]	1997	101	100	71*		92	24	7				
Tham *et al.*[29]	1994	45	58	44 (< 55)*			10		4			

CBD, common bile duct. *Mean; †median

Table 2a Summary of randomized controlled trials: endoscopic sphincterotomy

Reference	Year	No. of. patients	No. with CBD stones	Mean age (years)	Cannulation success (%)	Cholangiogram success (%)	Stones (%)	Therapeutic success (%)	Missed stones (%)	Duct clearance (%)	Retained stones (%)	Morbidity (immediate) (%)	Pancreatitis (%)	30-day morbidity (%)	Mortality rate (%)	Length of stay (days)
Neoptolemos *et al.*[30]	1987	55		61				96		91		16	4			9
Hammerstrom *et al.*[31]	1995	39		75				90			10	3	3	28	0	13
Targarona *et al.*[32]	1996	50	25	79	94	94	50	88	2	88		16	2	16	6	5
Sees and Martin[33]	1997	31	8	54				90					19			14
Rhodes *et al.*[34]	1998	40	40	68			100	75						15	2	4
Suc *et al.*[35]	1998	97						95			16	13			3	12
Cuschieri *et al.*[9]	1999	150	98		95		72	84		84		13	4		2	9

CBD, common bile duct

Table 2b Summary of randomized controlled trials: duct exploration

Reference	Year	No. of patients	Mean age (years)	Laparoscopic or open	Success rate (%)	Conversion rate (%)	Retained stones (%)	Morbidity rate (%)	Mortality rate (%)	Length of stay (days)
Neoptolemos *et al.*[30]	1987	60	59	Open	92		8	7	2	11
Hammerstrom *et al.*[31]	1995	41	74	Open	90		2	7	5	16
Targarona *et al.*[32]	1996	48	80	Open	96		2	8	4	11
Sees and Martin[33]	1997	51	51	Laparoscopic	100	20				10
Rhodes *et al.*[34]	1998	40		Laparoscopic	75	2		10	0	1
Suc *et al.*[35]	1998	105		Laparoscopic	100		6	4	1	16
Cuschieri *et al.*[9]	1999	150		Laparoscopic	83	13		16	1	6

Table 3 Medium-term complications of endoscopic sphincterotomy

Reference	Year	No. of patients	Length of follow-up (years)	Symptom-free (%)	Biliary symptoms (%)	Recurrent stones (%)	Papillary stenosis (%)	Ascending cholangitis (%)	Bile duct cancer (%)	Mortality rate (%)
Bergman *et al.*[36]	1996	94	15·0†			14	10			1
Sugiyama and Atomi[27]	1998	103	14·2*	90		8	7	5		
Tanaka *et al.*[37]	1998	410	10·1*			12	1	5	2	
Prat *et al.*[26]	1996	154	9·6*	88		2	2		2	
Hawes *et al.*[38]	1990	115	8·0*	83	11					
Tham *et al.*[29]	1994	30	8·0*	87	10		6	3		
Hammarstrom *et al.*[39]	1998	64	7·0†			5				
Wotjun *et al.*[19]	1997	483	6·0*		10	6	1	1		
Jacobsen and Matzen[40]	1987	96	4·1*	93	7	3		6		2
Testoni and Tittobello[41]	1991		4·0*	86		10				
Ikeda *et al.*[42]	1988	408	3·7*			6	7			
Greenfield *et al.*[43]	1985	25	3·0*	76						
Siefert *et al.*[11]	1982	9041		82		6	3			
Geenan *et al.*[44]	1998	2096	1·0*			2				

*Mean; †median

Table 4 Long-term complications of endoscopic sphincterotomy and biliary–enteric anastomosis

Reference	Year	Complication
Bergmann *et al.*[45]	1997	Permanent loss of sphincter function, bacterobilia and chronic inflammation
Sand *et al.*[46]	1992	Bacterobilia resulting in deconjugation of bile and formation of pigment stones
Kurumado *et al.*[47]	1994	Bacterobilia resulting in deconjugation of bile and formation of pigment stones
Gregg *et al.*[48]	1985	Bacterobilia resulting in deconjugation of bile and formation of pigment stones
Kurumado *et al.*[47]	1994	Biliary hyperplasia or atypia
Eleftheliadis *et al.*[49]	1988	Biliary hyperplasia or atypia
Tanaka *et al.*[37]	1998	Bile duct cancer
Prat *et al.*[26]	1996	Bile duct cancer
Strong[50]	1999	Bile duct cancer following biliary–enteric anastomosis
Hakamada *et al.*[51]	1997	Bile duct cancer following transduodenal sphincteroplasty
Tocchi *et al.*[52]	2001	Bile duct cancer following biliary–enteric drainage

methods, but with a slightly higher morbidity and significantly higher mortality rate (2 *versus* 1 per cent; $P = 0{\cdot}03$) for endoscopic sphincterotomy compared with laparoscopic exploration. No long-term results are yet available for laparoscopic bile duct exploration.

Discussion

A major difficulty in considering the literature reports is that there are frequently no clear definitions of patient populations, therapeutic success and complication rates. This means comparisons can be only approximate. Many trials involving laparoscopic surgery have been undertaken while the participating surgeons were relatively inexperienced and their methods have varied. This has probably also happened in some of the studies of laparoscopic bile duct exploration, including the randomized trials. The larger series of laparoscopic bile duct exploration including all-comers describe a consistent duct clearance rate of over 90 per cent; the randomized trials do not achieve this value.

Table 5 Summary of bile duct explorations

Reference	Year	No. of patients	Age (years)	Laparoscopic or open	Unsuspected CBD stone (%)	Success rate (%)	Conversion rate (%)	Retained stones (%)	Morbidity rate (%)	Mortality rate (%)	Length of stay (days)
Roukema *et al.*[53]	1986	1007		Open (1971–1980)				0	14	2	
Martin *et al.*[54]	1998	300	51†	Laparoscopic		90	4		7	0	2·0
Millat *et al.*[55]	1997	236		Laparoscopic	25	88	10	5	13	0	
Berci and Morgenstern[56]	1994	226	54‡	Laparoscopic	41		7	3	6	0	
Berthou *et al.*[57]	1998	220		Laparoscopic		95	1	3	9	2	7·8
Giurgiu *et al.*[58]	1999	217		Laparoscopic		97		4			
Millat *et al.*[59]	1996	189	68‡	Laparoscopic		81	10	4		0	
Paganini and Lezoche[60]	1998	161		Laparoscopic		98	2	8	9	1	
Drouard *et al.*[61]	1997	161		Laparoscopic		92		4	7	0	7·6
Dorman *et al.*[62]	1998	148	53‡	Laparoscopic		97	3	2	4	1	
Snow *et al.*[63]	1999	136		Laparoscopic	31	84	8		8	1	
Phillips *et al.*[64]	1994	130		Laparoscopic	37	93		3	17	1	3·7
Rhodes *et al.*[65]	1995	129	47†	Laparoscopic		96			5		
Phillips *et al.*[66]	1995	129		Laparoscopic		90	3	5	13	1	3·4/9·5*
Keeling *et al.*[67]	1999	120		Laparoscopic		89					
Millat *et al.*[68]	1995	115	69‡	Laparoscopic		87	10	3			
DePaula *et al.*[69]	1994	114		Laparoscopic		90	3	1	6	1	1·7
Paganini *et al.*[70]	1995	110	57‡	Laparoscopic	39	96	4	5	8	1	
Pappas *et al.*[71]	1990	100	53‡	Open (1982–1986)				5		0	
Lezoche *et al.*[72]	1996	100		Laparoscopic		96	4	5	7	1	
Petelin[73]	1993	86		Laparoscopic		97	1	2	9	1	1·9
Swanstrom *et al.*[74]	1996	77		Laparoscopic				1	5		
Petelin[75]	1993	77		Laparoscopic		96	1	3			1·9
Hawasli *et al.*[76]	2000	73		Laparoscopic		85		11			
Ido *et al.*[77]	1996	73		Laparoscopic		93	0	19	5	0	9·4
Stoker[78]	1995	64		Laparoscopic		94	6	5	9	0	2·8
Franklin *et al.*[79]	1994	60		Laparoscopic		97	3	0	2	2	2·8
Dion *et al.*[80]	1992	59		Laparoscopic			7	10	15	0	6·5/12·0*
Lieberman *et al.*[81]	1996	59		Laparoscopic		86	2	12	12	2	6·1
Khoo *et al.*[82]	1996	51		Laparoscopic		75	2	14	16	0	3·0

CBD, common bile duct. *Transcystic *versus* transducted exploration; †median; ‡mean

Better randomized trials are needed with a clear statement that results are based on an intention-to-treat basis; so far this has not usually been the case.

This review shows that endoscopic sphincterotomy has three main disadvantages. First, rates of stone clearance may be as low as 75 per cent, with a median of 91 per cent (although several centres report higher rates of up to 100 per cent). This failure rate is clinically significant, although it may not be noticeable as an average UK general surgical practice would experience only one or two failures each year. Second, although the complication rate of the procedure has decreased with greater experience, pancreatitis continues to be a problem in most series, with an incidence of up to 7 per cent and a mortality rate of 0·2–2·3 per cent[13,17,28]. This complication rate depends more on technical factors than on concurrent medical risk[16,83]. Preliminary results of a recent trial from Arnold *et al.*[84] show a 10 per cent incidence of pancreatitis, which accounts for most of the sphincterotomy-related complications. In an average district hospital performing 200 cholecystectomies per year this would result in one or two cases of pancreatitis per year, and possibly one death from this complication in 7–10 years. (This assumes that 10 per cent of patients undergoing laparoscopic cholecystectomy have bile duct stones.) Another report[11] demonstrates a higher risk of pancreatitis among young and otherwise healthy patients, although this is challenged by a report from Cetta *et al.*[85] refuting such risk when the sphincterotomy is performed by experts. Several attempts have been made to prevent pancreatitis, but with little success[86]. Laparoscopic bile duct exploration does not avoid pancreatitis, although this complication occurs only when instruments are passed through the sphincter of Oddi. To date, only a few cases have been reported, suggesting an incidence of about 1 per cent. Most series do not report pancreatitis as a problem.

As endoscopic sphincterotomy enters its third decade, medium- and longer-term results are now available and the third disadvantage is becoming apparent. Several centres have now published 10-year follow-up data. The late biliary complications include a disappointing rate of recurrent duct stones some years after sphincterotomy, without evidence of a plateau effect[37]. Endoscopic sphincterotomy alone produced inferior results when subjected to a randomized trial against open cholecystectomy and bile duct exploration[32], despite all the patients in the trial being at increased risk for open operation because of older age or coexistent medical conditions. The surgically treated patients had fewer late biliary complications. The retained gallbladder may have contributed to the biliary complications in the endoscopic group. A preliminary communication from Peppelenbosch *et al.*[87] described a 2 per cent bile duct stone rate at 10 years after open cholecystectomy with bile duct exploration, compared with a rate of 19 per cent after endoscopic sphincterotomy.

The sphincter of Oddi provides a barrier that prevents reflux from the duodenum into the bile duct, and biliary sphincter function is permanently lost after sphincterotomy[45]. A high rate of bacterobilia occurs after endoscopic sphincterotomy (up to 60 per cent), the result of duodenobiliary reflux[46,48]. Recurrent bile duct stones are soft brown calcium bilirubinate stones resulting from bacterial infection[88,89]. Confirmed duodenobiliary reflux and bacterial contamination of the bile ducts are responsible for the continuing duct stone formation with time[90]. The resultant clinical problem has led both Geenen *et al.*[44] and Ikeda *et al.*[42] to recommend annual ERCP and stone extraction in patients who have undergone sphincterotomy.

These circumstances are similar to those pertaining in the presence of duodenal diverticula, where an incompetent sphincter results in bacterial contamination of the bile ducts and formation of pigment stones due to bacterial deconjugation of bilirubin[91,92].

Once the barrier provided by the sphincter of Oddi is abolished, duodenobiliary reflux causes the biliary epithelium to adapt to a new environment. Kurumado *et al.*[47] produced varying degrees of bacterobilia in rodents by constructing biliary–enteric anastomoses. Examination of the mucosa showed hyperplasia in almost all cases, and epithelial atypia in two of six patients with a choledochojejunostomy. Eleftheliadis *et al.*[49] took gastroscopic biopsies of the bile duct mucosa 1–12 years after choledochoduodenostomy, and detected hyperplasia and intestinal metaplasia of the bile duct epithelium in all nine patients. Hyperplasia and intestinal metaplasia have been found frequently in the epithelium adjacent to gallbladder cancer[93]. The above studies raise the possibility that chronic bacterobilia may lead to neoplastic change in the biliary epithelium. Bile duct cancer rates as high as 7·4 per cent have been reported in several studies 10–30 years after biliary–enteric anastomosis and transduodenal sphincteroplasty[50,51]. Surgeons from Japan[37] and France[26] have recently reported cases of bile duct cancer occurring about 10 years after endoscopic sphincterotomy. Cholecyst-ectomy alone may protect against the development of bile duct cancer[94], so any rise noted after sphincterotomy must be taken seriously.

An anomalous pancreaticobiliary junction is present in nearly all patients with congenital choledochal cysts[95–97], a condition with a high incidence of malignancy[98]. The anatomical anomaly is frequently associated with biliary cancer without coexistent cyst formation. Abnormal reflux of pancreatic juice into the biliary tract occurs, reflected by the high amylase content of gallbladder bile in these cases. This enzymatic refluxate is activated in the bile ducts. Activated phospholipase A_2 has a directly proliferative effect on the gallbladder mucosa and, once activated, produces lysophosphatidylcholine, which has a cytotoxic effect. Both may cause mucosal hyperplasia and carcinoma of the gallbladder[95]. It is possible that destruction of the biliary sphincter by sphincterotomy may allow reflux of pancreatic juice into the bile duct, producing mucosal changes; further study is required.

It seems, therefore, that there is a good case for preserving the biliary sphincter in young patients with bile duct stones. If dividing the sphincter is to be avoided in order to preserve the physiological status of the biliary system, what reasonable alternatives are available? Endoscopic balloon sphincteroplasty has been used[99,100] with the hope that sphincter of Oddi function may recover, in contrast to the permanent destruction caused by sphincterotomy[101,102]. The reported incidences of postsphincteroplasty pancreatitis and persistent bacterobilia suggest no improvement over those for endoscopic sphincterotomy[48].

The alternative of supraduodenal exploration of the bile duct at open operation is safe and effective in fit patients[6]. Recent experience with laparoscopic common bile duct exploration outside randomized trials has demonstrated initial bile duct clearance rates consistently above 90 per cent; a few of the larger series are based on 'all-comers'. There is a consistently lower incidence of pancreatitis after laparoscopic exploration, compared with open exploration[103–105] which, when applied to larger numbers, should reduce the mortality rate in young fit patients. This would render the laparoscopic approach the preferred option, even after previous cholecystectomy[106]. For older or less fit patients the choice is more difficult and randomized trials are required to determine any advantage of one treatment over the other. The National Institutes of Health in the USA has examined the role of endoscopic sphincterotomy in the management of choledocholithiasis, and concluded that laparoscopic common bile duct exploration is more efficient and is preferable when surgical proficiency in this technique is available.

If such proficiency is not available, is open bile duct exploration to maintain a competent sphincter a good alternative? The results reported by Vellacott and Powell[1] in 1979 were poor: a 51 per cent negative exploration rate, 9 per cent retained stone rate and 7 per cent mortality rate. However, these results were achieved by inexperienced surgeons more than 20 years ago. Ten years later better results were reported: a negative exploration rate of 29 per cent, retained stone rate of 3 per cent and a mortality rate of 3 per cent[107]. Results from recent randomized trials with one arm as open duct exploration have suggested a 6 per cent retained stone rate and 1 per cent mortality rate for all age groups[108], and a 6 per cent retained stone rate and 4 per cent mortality rate for high-risk patients[32]. The results of both trials slightly favour open operation over endoscopic treatment. A population-based study from Pennsylvania completed in 1989 reported a mortality rate of 3·5 per cent in 5530 patients over 65 years old undergoing open cholecystectomy and exploration of the common bile duct; 28 per cent of these patients were over 80 years old[109]. High rates of duct clearance are required, avoiding surgical sphincterotomy or choledochoduodenostomy; choledochoscopy is probably the best method of achieving this objective[110].

Taking all the evidence into account, the authors conclude that laparoscopic exploration of the bile duct appears to be the best option overall for young fit patients. There may be a marginal advantage over endoscopic sphincterotomy in terms of mortality risk in the short term and possibly fewer late sequelae, although long-term follow-up studies are required to confirm any such effect. No such judgement can be made in respect of patients with co-morbidity adding to the operative risk; randomized trials are required to address the management of this group of patients.

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Review

Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes

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Background and methods: This review examines the various methods of detecting occult breast cancer metastasis in the sentinel lymph node (SLN). The prognostic relevance of such micrometastases and isolated tumour cells, and their impact on stage migration and decision making with respect to axillary dissection and adjuvant systemic therapy, are discussed.

Results: Examination of SLNs by serial section with haematoxylin and eosin and/or immunohistochemical staining significantly increases the detection rate of micrometastases, even in patients with very small (T1) tumours. However, the prognostic relevance of isolated tumour cells and small micrometastases is uncertain. Moreover, deciding which patients might benefit from axillary dissection is complicated by the fact that adjuvant radiotherapy and systemic chemotherapy alone may eradicate most micrometastases.

Conclusion: Ongoing randomized trials comparing the results of SLN biopsy alone with those of axillary dissection should answer the question of whether isolated tumour cells and small micrometastases are clinically relevant. This should also indicate which patients with SLN micrometastasis are likely to benefit from axillary dissection. In this sense, SLN biopsy must be considered still to be at an investigative stage; outwith clinical trials complete axillary dissection should be performed on all patients with SLN micrometastasis.

Paper accepted 13 August 2002

British Journal of Surgery 2002, 89, 1505–1515

Introduction

Axillary lymph node metastasis in patients with early breast cancer is the single most important prognostic factor for recurrence and survival, and forms the basis for important therapeutic decisions. However, about a quarter of all axillary node-negative patients have a relapse and/or die during the 5–10 years following diagnosis[1,2]. Extensive research has focused on prognostic indicators of the primary tumour in an attempt to replace lymph node evaluation, but none has equalled the predictive power of the lymph nodes[3]. It is worthy of note that the fact that lymph node status does not perfectly predict the likelihood of recurrence may depend not so much on the lymph node itself, but on the inadequacy of the techniques for examination. This is especially true for the single haematoxylin and eosin section, which probably evaluates less than 1 per cent of the lymph node[4]. Several studies using a combination of serial sectioning and immunohistochemical detection found metastases in 25–31 per cent of axillary node-negative patients[5,6]. Unfortunately, serial sectioning with immunohistochemistry (IHC) cannot be carried out routinely because it is too labour intensive and time consuming to be applied to 15–20 lymph nodes.

Sentinel lymph node (SLN) biopsy is emerging as an alternative to axillary dissection in the staging of patients with breast carcinoma. It allows the pathologist to focus on the small number of lymph nodes most likely to contain tumour. As experience with the technique has increased, however, new issues have arisen. Removed SLNs typically are examined with great thoroughness, significantly increasing the detection rate of micrometastases[7–9], even in patients with very small (T1) tumours. In this light it is important to assess the significance of SLN micrometastasis and, in particular, to define whether its presence indicates a need for axillary dissection in addition to adjuvant systemic therapy. This review was undertaken to examine the various methods of detecting occult metastasis in SLNs, the prognostic relevance of micrometastasis and isolated tumour cells, and their impact on stage migration and decision making for axillary dissection and adjuvant systemic therapy.

Definition of micrometastasis

The term 'axillary micrometastasis' was first introduced by Huvos *et al.*[10] in 1971. According to their definition, a micrometastasis is a metastatic deposit smaller than 2 mm in diameter detected in a single lymph node after extensive review of the original histological material. Any metastatic deposit of 2 mm or more in diameter, and/or any metastasis to two or more lymph nodes, is defined as macrometastasis. Use of the term micrometastasis for lesions smaller than 2 mm derives from data suggesting that lesions of this size are of no clinical significance[11]. This definition has been adopted by the Union Internacional Contra la Cancrum (UICC)[12] as well as the American Joint Commission on Cancer (AJCC)[13].

The term now encompasses tumour deposits down to a single cell and it is evident that the extent of micrometastasis varies, ranging from isolated single cells to large colonies of several thousand cells. It has been suggested that colonies of cells are clinically significant and that individual cells generally are not[4]. This implies that a subclassification of micrometastasis to distinguish micrometastasis from isolated tumour cells may be required[12]. In the tumour node metastasis (TNM) classification of the UICC[14], micrometastasis is defined as arrest and implantation of tumour cells in the organ involved, with extravasation, proliferation, and often a stromal reaction with a defined size of 2 mm or less. Isolated tumour cells are single tumour cells or small clusters of cells not more than 0·2 mm in greatest dimension, which do not typically show evidence of metastatic activity or penetration of vascular or lymphatic sinus walls. However, the TNM classification provides no solution on how to classify isolated tumour cells at multiple locations or multiple locations of micrometastases. Recently, the AJCC Breast Committee proposed that micrometastasis with a maximum size of 0·2 mm should be classified as isolated tumour cells pN0 (itc) and metastasis larger than 0·2 mm but smaller than 2·0 mm as micrometastases pN1 (mcm)[15]. As long as the prognostic relevance of isolated tumour cells has not been validated prospectively, adjuvant therapy should not be recommended to patients classified as pN0 (itc) with otherwise good prognostic factors. This general philosophy is similar to that put forward by others[4,15–17].

Various alternative definitions have been suggested: micrometastasis of less than 1·0 mm[18,19], micrometastasis involving less than 20 per cent of the lymph node sectional area[20], and even one differentiating between metastasis of less than 1·3 mm and metastasis of 1·3–2·0 mm in size[21]. Nevertheless, all proposed limits of the size of the nodal metastases are arbitrary until a survival analysis can be conducted with controlled data. Using relative rather than absolute criteria, Black *et al.*[20] defined micrometastases as less than 20 per cent involvement of the lymph node sectional area. However, this measurement is particularly arbitrary because of the great variety in lymph node size and enlargement owing to factors other than metastasis.

Impact of micrometastasis on survival

The clinical significance of micrometastatic disease remains controversial. The use of serial sectioning and IHC had already been tested in haematoxylin and eosin-negative nodes of complete axillary dissection specimens before the introduction of the SLN concept. Although some studies question the significance of metastatic deposits detected by such methods[5], nodal micrometastases appear to have a small but significant adverse effect on disease-free and overall survival in most series[22–29]. A review by Dowlatshahi *et al.*[11] showed that all studies that identified survival differences featured larger patient populations (range 147–921), a follow-up of at least 6 years or detection of occult lymph node metastases by IHC. This led these authors to conclude that such occult metastases have important prognostic implications and so may be important in terms of therapeutic decision making. In their study, however, the size of the occult metastases was not taken into account fully, even though this is clearly of major relevance.

It has been demonstrated that there is a linear correlation between the size of nodal metastasis and survival[5,6,30]. While it is unlikely that all tumour cells detected in SLNs are clinically significant, it is interesting that bone marrow micrometastases have recently been reported to have a negative impact on the survival of patients with early breast cancer[31]. It has long been known that individual malignant cells break away from the primary tumour and circulate in the bloodstream, but these cells do not necessarily have the ability to survive and grow at distant locations. It has been hypothesized that the presence of a large colony (more than ten cells) of metastatic cells in a SLN may be of prognostic importance, whereas perhaps a single malignant cell or a small group of cells (less than ten) may not[4]. Clinical trials to test this hypothesis are urgently needed.

The median size of micrometastases detected on cytokeratin IHC stains is approximately 0·1 mm, in contrast to 1·0 mm for haematoxylin and eosin staining[32]. It is uncertain, however, whether more accurate staging as a result of the detection of a single cell or a small group of malignant cells (less than ten) in SLNs will influence patient survival. What constitutes appropriate advice for patients whose SLN is haematoxylin and eosin negative but positive on IHC remains uncertain. The College of American Pathologists has affirmed that the prognostic and predictive value of micrometastasis identified in deeper sections using

IHC in SLNs is still unproven; basing therapeutic decisions on such findings is not recommended until further studies demonstrate their clinical significance[33].

Diagnosis of micrometastasis in sentinel lymph nodes

Histological examination of permanent sections: step sectioning with haematoxylin and eosin staining combined with immunohistochemistry

Conventionally, a lymph node examination is based on haematoxylin and eosin staining of one or two sections through the largest diameter of the lymph node. However, detection of micrometastasis by such routine histological examination of the SLN is unlikely. Extensive histopathological investigation, including step haematoxylin and eosin-stained sections[34–36] and IHC[37–42], is mandatory for the reliable detection of metastasis in SLNs. The incidence of SLN micrometastasis detected in this fashion is approximately 20 per cent in dissected axillary lymph node specimens that were thought to be tumour negative following standard pathological examination[34,37–42]. However, the large number of sections cut, sectioned and reviewed requires considerable work for the laboratory technician and pathologist, and IHC is more expensive than haematoxylin and eosin staining; a significant portion of the overall charge for SLN biopsy is allocated to pathological examination[43]. A method of high sensitivity with an acceptable workload for the pathologist would seem desirable but, even so, the minimal amount of histopathological evidence that needs to be obtained from the SLN remains unclear.

Fisher *et al.*[44] sectioned nodes at 5-μm intervals, detecting occult metastases in 24 per cent of patients, and concluded that 20-μm intervals were adequate because that was the average size of a tumour cell. In their study, the size of the metastases ranged from 0·1 to 1·3 mm, with a mean of 0·3 mm. Based on this information as well as cost effectiveness, Jannink *et al.*[36] considered that serial sectioning at 500-μm intervals with haematoxylin and eosin and immunohistochemical staining would be appropriate. In their study, the mean number of SLNs examined per case was 2·6, and the mean number of sections per node was 14, resulting in 36 sections (2·6 × 14) per case for review. However, Dowlatshahi *et al.*[4] suggested that most significant metastases would be found with cytokeratin staining at 250-μm intervals. Because the mean maximum dimension of a malignant ductal cell is 20 μm, a colony of more than 20–30 cells is likely to be detected on sections made at these intervals.

On the other hand, Turner *et al.*[39] examined ten levels at 40-μm intervals in 42 SLN-positive patients with a negative initial haematoxylin and eosin section. Using IHC for the first two levels of SLN examination, they found additional metastases in all but one patient. They concluded that the additional eight levels of examination did not significantly contribute to the detection of additional metastases. In this study, however, only 400 μm of the entire SLN was examined with ten levels at 40-μm intervals, which might not be sufficient for the detection of all metastases. Rather than using many sections at small intervals, it may be more efficient to use fewer sections at larger step intervals[45].

The likelihood of finding SLN micrometastasis correlates with the number of sections examined and the sectioning interval, although this was not supported by a study by Turner *et al.*[39]. Recently, Viale *et al.*[18] examined SLNs completely at 50-μm sectioning intervals and non-SLNs with three to six sections at 100–500-μm intervals. They found that increasing the sectioning interval from 50 to 290 μm may result in missing as many as 18 per cent of micrometastatic SLNs. This finding argues strongly against suggestions that it is sufficient to examine sections every 250 or 500 μm[4,45,46]. Since not all nodal metastases will be detected even with this intensive protocol, the question arises of whether one really needs to find all metastatic cells[4].

Giuliano *et al.*[38] reported that 26 of 68 tumour-involved SLNs had micrometastases only, 11 of which were identified by immunohistochemical staining for cytokeratin, but not by haematoxylin and eosin examination. Not surprisingly, the yield with IHC is higher than that with haematoxylin and eosin alone. IHC facilitates the detection of single metastatic cells, and dramatically speeds up the screening of the sections. The median size of micrometastases detected on cytokeratin IHC stains is approximately 0·1 mm, in contrast to 1·0 mm for haematoxylin and eosin staining[32]. These single metastatic cells must be distinguished, however, from mesenchymal cells, mesothelial cells, transfer (contamination) artefact, and benign transport of benign or malignant epithelium. Haematoxylin and eosin staining is helpful for the detection of artefacts and benign inclusions, although some investigators omit it when IHC is performed. When the initial SLN (step) sections with haematoxylin and eosin staining are all negative, however, serial sectioning and IHC is recommended[38–40]. Nevertheless, one of the limitations of widespread use of these detailed techniques is the prohibitive labour costs. Moreover, because of observer variation, more than one pathologist may need to analyse the results of modern techniques to quantify micrometastatic status appropriately[16].

Intraoperative examination using frozen sectioning and/or imprint cytology

Intraoperative examination of the SLN for breast cancer staging is worthwhile because patients with SLN metastasis (approximately 25–30 per cent) may undergo immediate axillary dissection and be spared a separate operation[47,48]. The two techniques in current use for rapid diagnosis are imprint cytology with touch preparations of the SLN cut surface and frozen-section examination.

Several investigators have examined the value of frozen sectioning for the intraoperative assessment of SLNs. The main advantage is the visualization of nodal architecture. Disadvantages include frozen-tissue artefacts, consumption of some tissue, a slight time delay and frozen-tissue artefacts on subsequent paraffin sections. In early studies[49–54] the sensitivity range for frozen-section examination of the SLN was only 64–74 per cent, but reliability has improved[55,56]. In a study by Noguchi *et al.*[55], SLNs were bisected and sections were taken from each face of the node during the first phase of the study. During the second phase of the study at least three sections were obtained from each SLN at different levels. Each SLN was then serially sectioned at approximately 2-mm intervals during the third phase of the study. Results indicated that the sensitivity of frozen sectioning was 60 per cent in the first phase, 85 per cent in the second phase and 100 per cent in the third phase. Viale *et al.*[56] examined the SLN more deeply, sectioning frozen nodes subserially at 50-µm intervals. For each SLN, one section was stained with haematoxylin and eosin and the other was immunostained for cytokeratins with a rapid immunohistochemical assay, resulting in an overall accuracy of 97 per cent, a sensitivity of 93 per cent and a specificity of 100 per cent (*Table 1*). The authors concluded that extensive intraoperative examination of SLNs by means of frozen-section examination could attain a sensitivity similar to that of routine histological examination without intraoperative frozen sectioning. However, such multiple sectioning is time consuming, and is especially problematic for routine use in small hospitals with few personnel.

Examination by imprint cytology may be useful for determining the status of SLNs during operation because multiple cut surfaces can be examined quickly[52,57]. Advantages include excellent cytological detail, speed and preservation of tissue for paraffin-section histopathology. Disadvantages include fewer cells for examination and a higher chance of indeterminate results (atypical or suspicious cells) compared with frozen-section examination. In a study by Van Diest *et al.*[58] SLNs smaller than 10 mm in diameter were halved, and larger nodes were laminated into 5-mm pieces. Imprints were then made of all cut surfaces and stained. This resulted in a sensitivity of 62 per cent and a specificity of 100 per cent. Ratanawichitrasin *et al.*[59], on the other hand, divided SLNs in two if the diameter was less than 8 mm, or cut them into multiple sections 3 mm thick if the diameter was greater than 8 mm. They reported a sensitivity of 82 per cent and a specificity of 100 per cent for determining the status of the SLN. In a study by Motomura *et al.*[60], SLNs of 4 mm or more in diameter were serially sectioned at 2-mm intervals, and smaller nodes were

Table 1 Intraoperative diagnosis of sentinel lymph node metastasis

				Prediction of axillary lymph node metastasis		
Reference	Year	No. of sections	No. of patients	Accuracy (%)	Sensitivity (%)	Specificity (%)
Haematoxylin and eosin staining of frozen section						
Veronesi *et al.*[49]	1997	At least three sections	107	83	64	100
Noguchi *et al.*[50]	2000	At least one section	425	90	72	100
Canavese *et al.*[54]	1998	6 sections	96	91	73	100
Noguchi *et al.*[55]	2000	2 sections	38	79	60	100
		> 3 sections	45	93	85	100
		2-mm interval	26	100	100	100
Haematoxylin and eosin staining and IHC of frozen section						
Viale *et al.*[56]	1999	50-µm interval	117	97	93	100
Imprint cytology						
Cserni[61]	2001	2 sections	60	—	59	100
Rubio *et al.*[57]	1998	2 sections	53	99	96	100
Van Diest *et al.*[58]	1999	< 5-mm interval	59	83	62	100
Ratanawichitrasin *et al.*[59]	1999	3–4-mm interval	55	95	82	100
Motomura *et al.*[60]	2000	2-mm interval	101	96	91	99

IHC, immunohistochemistry

bisected. They reported a sensitivity of 91 per cent and a specificity of 99 per cent, although the results of imprint cytology were compared only with those of IHC (*Table 1*).

Thus the sensitivity of SLN diagnosis based on imprint cytology[57,59–61] and frozen-section examination[54–56] is related to the number of sections performed through the node. It is unreasonable to expect that either method will detect every metastatic deposit seen on permanent serial sections or by IHC.

Reverse transcriptase–polymerase chain reaction analysis

In recent years, several groups have used reverse transcriptase–polymerase chain reaction (RT–PCR) to improve further the detection of SLN metastasis beyond that achievable by serial sectioning and IHC[62–64]. Min *et al.*[65] evaluated seven potential breast cancer tumour markers for expression in human breast cancer adenocarcinoma lines and in normal nodes from patients without cancer. Of these seven markers, mammaglobin transcripts were detected in 100 per cent and carcinoembryonic antigen (CEA) transcripts in 71 per cent of breast adenocarcinoma lines, and were absent from all normal lymph nodes. These authors suggested that these markers should be used as components of a multimarker panel to evaluate SLNs in an ongoing multicentre clinical trial. Subsequently, Kataoka *et al.*[62] examined SLNs by using RT–PCR analysis for CEA and mammaglobin. They found CEA expressed in 25 per cent of 48 patients with haematoxylin and eosin-negative SLNs, and mammaglobin in 21 per cent. While haematoxylin and eosin staining of SLNs could predict axillary lymph node status with an accuracy of 95 per cent and false-negative rate of 6 per cent, RT–PCR improved these results to 99 and 3 per cent respectively. The authors concluded that RT–PCR analysis is a powerful and sensitive method of SLN diagnosis.

However, there is as yet no clearly defined RT–PCR marker or set of markers for breast cancer[46], unlike melanoma for which the tyrosinase marker has clearly been identified as specific and reliable for the detection of micrometastasis. Recent work suggests that up to 20 per cent of breast cancers do not express mammaglobin at all[64,66,67], and the prognostic significance of micrometastasis detected with this new technique and of the tumour markers themselves has not yet been determined[68,69]. Furthermore, the usefulness of the technique, which can detect one malignant cell in one million lymphocytes[70], two orders of magnitude greater than that attained with haematoxylin and eosin staining, requires further evaluation as the test may be just too sensitive to be clinically useful[34,36,71]. It seems unlikely that the majority of such malignant cells would escape immune surveillance and acquire the traits necessary to become clinically important. Thus, the RT–PCR method requires further evaluation, even though it has the potential to improve the sensitivity of SLN biopsy[65]. Long-term prospective studies should determine whether patients with breast cancer with lymph node metastases detected by RT–PCR molecular assay are at increased risk of subsequent disease relapse. One such study, the American College of Surgeons Oncology Group Z0010 trial, is currently under way and should provide an answer to this question within the next 5–10 years.

Non-sentinel lymph node metastasis in patients with micrometastasis in sentinel lymph nodes

It is clinically relevant to evaluate the distribution of metastases in SLNs and non-SLNs because an overview study has shown that 38–67 per cent of patients with breast cancer and positive SLNs have no disease in other non-SLNs[72]. This finding not only strongly supports the SLN concept, but also suggests that axillary dissection can be avoided in such patients. Several investigators[8,9,32,40] have

Table 2 Non-sentinel lymph node metastasis according to size of primary tumour and size of sentinel lymph node metastasis

			Incidence of non-SLN metastasis	
Reference	Year	Tumour size	SLN micrometastasis ($\leqslant$ 2·0 mm)	SLN macrometastasis ($\geqslant$ 2·1 mm)
Czerniecki *et al.*[40]	1999	T1	0 of 5	2 of 2
		T2	3 of 4	3 of 4
Chu *et al.*[8]	1999	T1	2 of 46	19 of 40
		T2	2 of 20	20 of 38
		T3	1 of 3	9 of 11
Reynolds *et al.*[9]	1999	T1	0 of 18	9 of 18
		T2	6 of 9	13 of 15
Viale *et al.*[18]	2001	T1	20 of 93	—
		T2	4 of 17	—

SLN, sentinel lymph node

Table 3 Ongoing randomized clinical trials of sentinel lymph node biopsy

Clinical trial	Methods	Purpose or hypothesis
University of Vermont/NSABP study (Krag DN/1998)[76]	If SLN negative by H&E, randomize to ALND or SLN biopsy only	Local and distant recurrence after SLN biopsy alone Morbidity of SLN biopsy *versus* ALND
American College of Surgeons Oncology Group (Z0010) (Giuliano AE/1998)[82]	If SLN negative by H&E, no ALND; if SLN positive, offer randomization to Z0011	Axillary recurrence if SLN negative by H&E Prevalence and prognostic significance of IHC-positive cells in SLN and bone marrow
American College of Surgeons Oncology Group (Z0011) (Giuliano AE/1998)[82]	If SLN positive by H&E, randomize to ALND *versus* no ALND	Relative morbidity of SLN biopsy *versus* SLN biopsy + ALND Local and distant recurrence with and without ALND
ALMANAC trial (Clarke D/2001)[75]	If SLN negative by H&E, no ALND; if SLN positive, randomize to ALND or axillary radiotherapy	Local recurrence after SLN biopsy alone Morbidity and cost of SLN biopsy *versus* ALND
EORTC[77]	If SLN positive by H&E, randomize to ALND *versus* axillary radiotherapy	Both treatment modalities will result in the same degree of regional control and survival

NSABP, National Surgical Adjuvant Breast and Bowel Project; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; EORTC, European Organisation for Research on Treatment of Cancer; H&E, haematoxylin and eosin staining; ALND, axillary lymph node dissection; SLN, sentinel lymph node

examined the incidence of non-SLN metastasis in patients with SLN metastasis. They found that micrometastasis existing solely in SLNs of patients with clinically lymph node-negative T1 disease correlated with the absence, or low prevalence, of metastasis in other non-SLNs. While the number of patients in these studies was small[8,9,40] (*Table 2*), this suggests that it may be possible to treat patients with T1 tumours and SLN micrometastasis with SLN biopsy alone, avoiding unnecessary axillary dissection[40]. In other words, extensive searching of nodes would be unnecessary, thereby reducing the cost of pathological examination[73].

Turner *et al.*[32] reported that only 24 (26 per cent) of 93 patients with micrometastasis in the SLN had non-SLN metastasis. They found that the size of SLN metastasis, extranodal hilar tissue invasion (HTI), the size of the primary tumour and peritumoral lymphatic vascular invasion (LVI) were associated significantly with non-SLN metastasis. In their study, only one patient (2 per cent) had non-SLN metastasis among the 58 whose SLN micrometastasis was associated with the presence of T1 or T2 tumours, and the absence of LVI and extranodal HTI. They concluded that patients with such primary tumours and SLN findings may not require further axillary dissection.

Viale *et al.*[18] recently examined more patients with micrometastatic SLNs, and examined SLNs and non-SLNs more thoroughly. They reported that 25 per cent of patients with pT1c tumours and 24 per cent of those with pT2 tumours with micrometastatic SLNs had involvement of non-SLNs (*Table 2*). This is consistent with the previously mentioned findings of Turner *et al.*[32], who re-examined their results by performing two-level cytokeratin immunostaining on negative non-SLNs by means of standard haematoxylin and eosin staining. Nevertheless, the proportion of non-SLN involvement was significantly different for patients with SLN micrometastases measuring 1 mm or less and those with larger micrometastases (16 *versus* 36 per cent; $P = 0.02$). Outwith clinical trials, therefore, axillary dissection should be performed on all patients with breast cancer who show micrometastasis in the SLN[18].

Prospective randomized clinical trials

Five large randomized trials are currently in progress to evaluate certain aspects of SLN biopsy (*Table 3*). Since serial sectioning and IHC are not a part of these studies, it can be anticipated that a significant number of occult lymph node metastases will be missed. However, it is important to note that in all these trials systemic adjuvant treatment can be administered on the basis of conventional criteria, such as nodal status and primary tumour characteristics. Determining which patients with SLN metastasis may benefit from axillary dissection is complicated by the fact that the therapeutic benefits of adjuvant radiotherapy and systemic chemotherapy, which may eradicate most micrometastases, must be taken into account[74]. It is therefore not known whether SLN biopsy will increase the axillary recurrence rate and/or reduce overall survival. These important questions can be answered only by the results of these ongoing randomized prospective trials[70,75–77].

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, one group of patients will undergo SLN biopsy followed immediately by axillary dissection. A second group will undergo SLN biopsy and, if intraoperative examination results are negative, they will have no further surgical treatment. Patients who are found to be SLN positive during operation and those in whom an

SLN has not been identified will undergo axillary dissection. Patients who appear to be SLN negative during operation, but on further pathological review are found to be SLN positive, will undergo delayed axillary dissection. The NSABP trial is primarily testing whether there is excess morbidity (local failure in axilla, reduced disease-free and overall survival) when an SLN biopsy is used as the only axillary staging procedure if the SLN is found to be histologically negative by routine pathological evaluation (given that the unresected non-SLNs of some SLN-negative patients – estimated at 10 per cent – will carry disease). A secondary aim of the study is to evaluate the clinical significance of occult micrometastasis by utilizing the same clinical endpoints. Approximately 4000 patients will be enrolled in this study[70,76].

In trials of the American College of Surgeons, patients with negative SLNs are followed without axillary dissection (Z0010), and those with positive SLNs are randomized to either axillary dissection or no further axillary therapy (Z0011). This latter study does not use stratification with regard to the size of the metastasis identified in the SLN. In other words, a patient with a 2-cm metastasis could be randomized to observation alone and a patient with a 2-mm metastasis to axillary dissection. The Z0010 trial is a registration trial (no randomization), and patients with positive SLNs are offered participation in Z0011 (axillary dissection *versus* observation) whereas patients with negative SLNs are observed. However, the nodes of the latter group will be further examined pathologically in a fashion similar to that in the NSABP B-32 trial in order to determine whether occult micrometastasis affects survival and local recurrence[70,76].

In the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial[75], 1500 patients with a clinically negative axilla are randomized to axillary dissection or SLN biopsy. Patients with positive SLNs (based on paraffin-section histology) proceed to axillary dissection or axillary radiotherapy, and patients with negative SLNs have no further treatment to the axilla. The primary endpoints in this trial are axillary morbidity, and health economics of a SLN biopsy compared with axillary dissection. A secondary goal is to observe the axillary recurrence rate in patients with negative SLNs, thereby evaluating the clinical significance of occult metastases.

In a trial of the European Organisation for Research on Treatment of Cancer (EORTC)[77], 3000 patients with a clinically negative axilla but positive SLN will be randomized to axillary dissection or axillary radiotherapy. This is an equivalent study, in which it is hypothesized that both treatment modalities will result in the same degree of regional control and survival. If the outcome of the study shows that there is no difference in the two arms, patients with positive SLNs will be treated more frequently with axillary radiotherapy than axillary dissection, particularly when micrometastasis in SLNs is missed by intraoperative examination.

Elimination of axillary lymph node dissection as a result of sentinel lymph node biopsy

Recent studies have demonstrated that SLN biopsy is as accurate as axillary dissection for the assessment of the axilla in patients with T1–2 tumours[49,50,78–81]. Routine axillary dissection can be avoided in patients with node-negative breast cancer if there is extensive experience and a low false-negative rate with the technique in the hands of a particular surgeon and hospital team. The growing demand from patients for less invasive procedures has created considerable incentive for accepting SLN biopsy without axillary dissection as standard practice. However, a false-negative SLN biopsy is of great concern, potentially resulting in either axillary relapse or an incorrect decision about systemic treatment. Several studies[82–86] provide data on patients who underwent an SLN dissection as a sole procedure.

Giuliano *et al.*[82] reported no local or axillary recurrence at a median follow-up of 39 months in 67 SLN-negative patients who did not have axillary dissection. Similarly, Schrenk *et al.*[84] reported no axillary recurrence at a median follow-up of 22 months in 83 patients with negative SLN biopsy alone. In a study by Roumen *et al.*[85], only one of 100

Table 4 Observational studies on elimination of axillary lymph node dissection resulting from sentinel lymph node biopsy

Reference	Year	Status of SLN	No. of patients	Median follow-up (months)	Axillary relapse
Roumen *et al.*[85]	2001	Negative	100	24	1
Schrenk *et al.*[84]	2001	Negative	83	22	0
Giuliano *et al.*[82]	2000	Negative	67	39	0
Noguchi[86]	2001	Negative	196	Variable	0

SLN, sentinel lymph node

patients with a negative SLN biopsy result without axillary dissection showed an axillary relapse at a median follow-up of 24 months. In an overview of the Japanese experience, Noguchi[86] reported that none of 196 patients who had a negative SLN biopsy result without axillary dissection had an axillary relapse. Although the follow-up is short in these studies, SLN biopsy alone for node-negative breast cancer had no detrimental impact on the axillary failure rate (*Table 4*). It must be remembered, however, that adjuvant therapy may in part be responsible for the lack of axillary failure in patients with tumour-negative SLNs[87–89]. Since there is a known false-negative rate for SLN biopsy, it can be assumed that performing SLN biopsy alone must fail to remove the disease completely from the axilla in some patients in these observational studies[90]. In this sense, SLN biopsy must be considered still to be in the investigative stage until further work demonstrates the clinical significance of micrometastasis in SLNs.

Conclusion

Resected SLNs are typically examined with great thoroughness, thereby significantly increasing the detection rate of micrometastasis, even in patients with very small (T1) tumours. In the past decade, large studies with adequate follow-up have demonstrated consistently that such metastasis has important prognostic implications and so may be important in therapeutic decision making. However, it is not clear how extensively SLNs should be evaluated, because it is unlikely that all tumour cells detected in SLNs are clinically significant. Determining which patients with SLN micrometastasis may benefit from axillary dissection is complicated. That the therapeutic benefits of adjuvant radiotherapy and systemic chemotherapy may eradicate most micrometastases must be taken into account. Moreover, extensive histological examination of a SLN is expensive and requires considerable effort from the laboratory technician and pathologist. In the light of this, micrometastasis in the SLN warrants further investigation as SLN biopsy is likely to evolve into a diagnostic standard for breast cancer management. Ongoing randomized trials comparing SLN biopsy alone with axillary dissection should answer the principal following questions. (1) Are isolated tumour cells and small micrometastases clinically relevant? (2) Which patients with SLN micrometastasis will benefit from axillary dissection? The clinical significance of occult metastasis should be determined by long-term follow-up studies. At present, SLN biopsy must be considered to be at an investigative stage. Outwith clinical trials, complete axillary dissection should be performed on all patients with breast cancer who have micrometastasis in SLNs.

Acknowledgements

This study was supported by a grant for Scientific Research Expenses for Health and Welfare Programmes (Second Term Comprehensive 10-year Strategy for Cancer Control) from the Ministry of Health and Welfare, Japan.

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Meta-analysis of relaparotomy for secondary peritonitis

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Background: Planned relaparotomy and relaparotomy on demand are two frequently employed surgical treatment strategies for patients with abdominal sepsis.

Methods: The available literature was evaluated to compare the efficacy of both surgical treatment strategies. A systematic search for studies comparing planned and on-demand relaparotomy strategies in adult patients with secondary peritonitis was employed. Studies were reviewed independently for design features, inclusion and exclusion criteria, and outcomes. The primary outcome measure was in-hospital mortality.

Results: No randomized studies were found; eight observational studies with a total of 1266 patients (planned relaparotomy, 286; relaparotomy on demand, 980) met the inclusion criteria and were included in the meta-analysis. These eight studies were heterogeneous on clinical and statistical grounds ($\chi^2 = 40{\cdot}7$, d.f. = 7, $P < 0{\cdot}001$). Using a random-effects approach, the combined odds ratio for in-hospital mortality was 0·70 (95 per cent confidence interval 0·27 to 1·80) in favour of the on-demand strategy.

Conclusion: The combined results of observational studies show a statistically non-significant reduction in mortality for the on-demand relaparotomy strategy compared with the planned relaparotomy strategy when corrected for heterogeneity in a random-effects model. Owing to the non-randomized nature of the studies, the limited number of patients per study, and the heterogeneity between studies, the overall evidence generated by the eight studies was inconclusive.

Presented to the annual meeting of the Association of Surgeons of The Netherlands, Veldhoven, The Netherlands, May 2001, and to the annual meeting of The Netherlands Society of Gastroenterology, Veldhoven, The Netherlands, March 2002

Paper accepted 13 August 2002

British Journal of Surgery 2002, **89**, 1516–1524

Introduction

Secondary peritonitis or abdominal sepsis is still associated with a high mortality rate of around 30 per cent, despite improvements in antibiotic treatment and intensive care facilities. Surgical treatment of secondary peritonitis is usually threefold, consisting of a laparotomy to eliminate the source of infection, peroperative peritoneal lavage to reduce bacterial load, and the prevention of persistent or recurrent infection. The last of these may be established by continuous postoperative peritoneal lavage, by leaving the abdomen open (laparostomy), or by a repetitive planned or on-demand relaparotomy strategy. Continuous postoperative lavage has failed to gain wide acceptance[1]. On the other hand, the planned and on-demand strategies are commonly used for patients with intra-abdominal infection[2–6].

The main advantages of planned relaparotomy are early detection of persistent infection or infectious complications (potentially beneficial to patient outcome) and limited adhesion formation during early relaparotomy (possibly reducing the risk of surgical complications). The advantage of relaparotomy on demand is that the procedure is limited to patients who do in fact need such treatment, preventing unnecessary operations when infection has resolved during conventional postoperative treatment. Furthermore, the on-demand strategy provides a time lapse that may allow the development of a contained infection accessible to percutaneous interventional techniques. This meta-analysis compared the effect of planned relaparotomy and relaparotomy on demand in patients with secondary peritonitis.

Patients and methods

Inclusion and exclusion criteria

For inclusion, studies were required to assess patients undergoing either a planned relaparotomy or relaparotomy on demand strategy after an initial laparotomy for secondary peritonitis, and they had to compare the planned with the on-demand strategy. In addition, in-hospital mortality data were required to be available. Articles on continuous ambulatory peritoneal dialysis (CAPD) peritonitis, peritonitis due to pancreatitis, and peritonitis in patients aged less than 18 years were excluded. CAPD peritonitis was excluded because the treatment is primarily conservative (antibiotics) and surgical treatment usually consists simply of removal of the CAPD catheter. Pancreatitis was excluded because of its initially non-infectious aetiology and the primarily non-operative treatment, although planned reoperations are performed for debridement of (infected) pancreatic necrosis[7–9]. No restrictions were applied to methodological criteria, but an evaluation of the relationship between methodological quality and outcome was undertaken.

The planned relaparotomy strategy required a decision to be made during the initial operation for secondary peritonitis to perform one or more relaparotomies every 1–3 days until no residual infection was found. The on-demand relaparotomy strategy required the performance of a relaparotomy after the initial laparotomy for peritonitis only when the clinical condition of a patient deteriorated or failed to improve. The index operation was defined as the initial laparotomy of a patient for secondary peritonitis. Secondary peritonitis was defined as intra-abdominal sepsis caused by perforation, infection, ischaemia or necrosis of part of the digestive tract or visceral organ, or peritonitis due to a postoperative complication.

Search strategy

Two authors (B.L., M.A.B.) independently performed a formal computer-assisted search of the medical databases Medline (January 1966 to January 2001, search updated until January 2002), Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Register, Database of Abstracts on Reviews and Effectiveness, Current Controlled Trials, and Embase (January 1988 to January 2001). Keywords and medical subject heading (MeSH) terms used were 'abdominal sepsis', 'secondary peritonitis', 'relaparotomy' and 'planned relaparotomy'; English and German clinical studies were identified. A manual cross-reference search of the eligible papers was performed to identify additional relevant articles. No unpublished data or data from abstracts were encountered or used.

Data collection

Three authors (B.L., M.A.B., J.B.R.) independently assessed selected studies and extracted data on methodology, level of evidence, population, intervention and outcome measures, and judged whether the publication met the stated inclusion criteria. The methodological quality of studies was initially evaluated using the Levels of Evidence for studies on therapies of the NHS Research and Development Centre for Evidence Based Medicine, Oxford, UK (http://www.cebm.jr2.ox.ac.uk), as originally developed by the Canadian Task Force on the Periodic Health Examination[10] in 1979.

Some key methodological issues were assessed in more detail. The allocation of a particular treatment strategy was assessed for randomization; timing and criteria used. Retrospective, prospective and secondary prospective collection of data were analysed, as well as potential adjustment for differences in prognosis. Retrospective data were defined as data extracted from patient charts or routine data sources. Prospective data were defined as specific information whose accumulation started before the index operation in specifically identified patients. Secondary prospective data were defined as for prospective data, but originating from another study or from an ongoing register.

Adjustment for differences in prognosis at the time of the index operation (baseline) was performed by design (randomization or matching), by statistical analysis (stratified analysis or modelling technique) or by exclusion of subgroups. Data on secondary outcome measures were retrieved from the included studies. Disagreements about the inclusion of studies and data extraction were resolved by group discussion. The reporting checklist proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group[11] was used as a guideline when performing this meta-analysis. Observational studies were defined as effectiveness studies using data from existing databases, cross-sectional studies, case series, case–control studies, or studies with a historical control or a cohort design[11,12].

Statistical analysis

The primary outcome measure was the odds ratio (OR) for in-hospital mortality in the individual studies. An OR of less than 1 signifies a higher risk of dying from the planned relaparotomy than from the on-demand relaparotomy strategy. Statistical heterogeneity of the included studies was assessed with the χ^2 test with $k - 1$ degrees of freedom. Estimates of the efficacy of therapies were expressed as pooled ORs using either the fixed-effects model (according to Mantel–Haenszel)[13] or the random-effects model (according to DerSimonian–Laird)[14], depending on the degree of heterogeneity of the included studies. When significant heterogeneity was found, the random-effects method was used to calculate the pooled OR. P values were calculated with the χ^2 or Fisher exact test as appropriate;

$P < 0.05$ was considered statistically significant. Data analysis was performed using Review Manager 4·1 software (Cochrane Collaboration, Oxford, UK) and Statistical Package for the Social Sciences version 9·0 (SPSS®, Chicago, Illinois, USA).

Results

Excluded studies

The initial search yielded 181 articles, of which 161 did not meet the inclusion criteria (*Fig. 1*). The majority of excluded papers covered topics such as indications, diagnostic modalities and scoring systems for peritonitis or relaparotomy. Other excluded articles were review articles, articles on prognostic variables not including data on treatment strategy, those that compared antibiotic strategies or different lavage fluids, and those on treatment strategies for acute pancreatitis. Retrieval and assessment of the 20 candidate papers led to exclusion of a further three[15–17] because of insufficient data on the primary endpoint, and exclusion of another nine because planned relaparotomy[1,6,18–23] or relaparotomy on demand[24] was assessed in isolation, without comparison to the other strategy. No randomized clinical trial or level I evidence was encountered during the search of the literature.

Included studies

The eight articles[25–32] included in the meta-analysis are depicted chronologically in *Table 1*. The total number of patients in these studies was 1266 (planned relaparotomy,

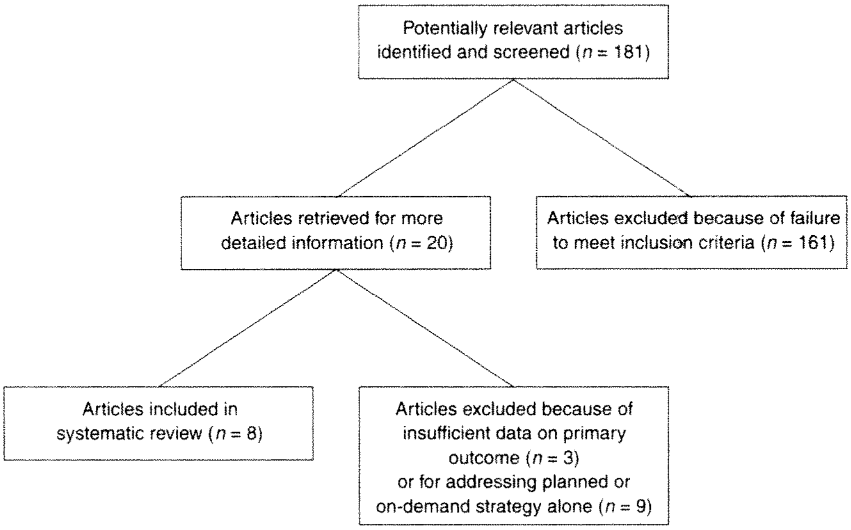

Potentially relevant articles identified and screened (n = 181)
Articles retrieved for more detailed information (n = 20)
Articles excluded because of failure to meet inclusion criteria (n = 161)
Articles included in systematic review (n = 8)
Articles excluded because of insufficient data on primary outcome (n = 3) or for addressing planned or on-demand strategy alone (n = 9)

Fig. 1 Number of articles identified and evaluated during the review process

Table 1 General characteristics of included studies involving 1266 patients

Reference	Year	Country	No. of hospitals	Inclusion period	No. of patients Planned (n = 286)	On demand (n = 980)
Penninckx *et al.*[30]	1983	Belgium	1	Not given	31	11
Andrus *et al.*[25]	1986	USA	1	1980–1985	34	43
Penninckx *et al.*[31]	1990	Belgium	1	Not given	44	9
Wittmann *et al.*[32]	1994	USA	12	1987	95	260
Hau *et al.*[27]	1995	Germany, Switzerland, Austria	18	1992–1993	38	38
Koperna and Schulz[28*]	1996	Austria	1	1992–1995	9	83
Grunau *et al.*[26]	1996	Germany	1	1989–1993	13	35
Koperna and Schulz[29*]	2000	Austria	1	1986–1996	22	501

*Different hospitals involved

286; relaparotomy on demand, 980), in whom 283 deaths (101 and 182 respectively) occurred. The median (range) number of patients in the on-demand strategy groups was 41 (9–501), which was higher than that of 33 (9–95) in the planned relaparotomy groups.

Clinical characteristics

The median ages in the planned and on-demand groups were similar: 53·8 and 54·0 years respectively. The male : female ratio was 1·06 in the relaparotomy on demand group and 0·87 in the planned relaparotomy group. The severity of disease was expressed by means of the Acute Physiology And Chronic Health Evaluation (APACHE) II score in four studies[26–28,32] and as an Acute Physiology Score (APS) in one study[25]. The median (range) APACHE II score was higher in the planned relaparotomy group at 15·9 (10·0–17·6) than in the on-demand relaparotomy group at 10·5 (10·0–11·8), as was the APS (21·0 *versus* 18·0). One study[31] calculated the Mannheim Peritonitis Index (MPI) score and reported similar scores for the planned and on-demand strategies (32·4 and 32·2 respectively).

Specific clinical and design characteristics of the included studies are shown in *Table 2*. The treated population ranged from patients with severe generalized peritonitis to those with intra-abdominal infection due to a postoperative complication. The median (range) percentage of patients with postoperative peritonitis was 33·6 (18·2–43·2) per cent in the planned relaparotomy group and 31·1 (9·2–51·2) per cent in the on-demand group. The median (range) percentage of patients in whom elimination of the focus of the peritonitis was successful was 86·8 (46·2–100) per cent in the planned relaparotomy group and 88·6 (86·8–89·2) per cent in the on-demand group, but this was assessed in only three studies. Two studies[25,30] excluded patients with appendicitis as a causative focus of peritonitis, whereas Koperna and Schulz[28] excluded patients with primary, pancreatic or traumatic peritonitis. In three studies no well described definition was available for the relaparotomy on demand strategy. The time interval between index operation and relaparotomy in the planned relaparotomy group in the various studies ranged from 24 h to 3 days.

Design

Assessment of the allocation of the treatment strategy showed that there were no randomized studies included in this meta-analysis (*Table 2*). Timing of allocation of the treatment strategy was at the time of the index operation in all but one study (in which timing was unclear). When the decision for a particular treatment strategy was made at the index operation, two studies reported explicit clinical criteria for the choice of treatment strategy, and in two studies the allocation was performed by surgeon (one study) or by institution (one study). In the majority of studies no details were provided on the allocation criteria used. Data collection was performed retrospectively in three studies, prospectively in three studies and secondarily prospectively in two. Adjustment for differences in prognosis was performed by exclusion of subgroups in two studies, and by stratified analysis, statistical modelling and design through matching in one study each. No adjustment for prognosis was performed in three studies.

Mortality

Mortality was expressed as in-hospital deaths in all reports. The median (range) mortality rate in the eight studies was 33 (21–77) per cent for the planned strategy and 22 (12–89) per cent for the on-demand strategy. The relative risk of both treatment strategies in individual studies ranged from 6 to 78 per cent. The test for heterogeneity of the included studies was highly significant (χ^2 = 40·7, d.f. =7, P < 0·001). The effectiveness of both treatment strategies, as measured by in-hospital mortality rate, resulted in a pooled OR of 0·70 in favour of the relaparotomy on demand strategy, but with a large 95 per cent confidence interval (c.i.) ranging from 0·27 to 1·80 (P = 0·5) using the random-effects model (*Fig. 2*). Stratified analysis of the five prospective studies[25–28,32] produced an OR of 0·52 (95 per cent c.i. 0·27 to 1·00; P = 0·05). The four studies[26–29] published from 1995 onwards produced an OR of 0·21 (95 per cent c.i. 0·09 to 0·53; P < 0·001). All other stratified analyses revealed no significant results.

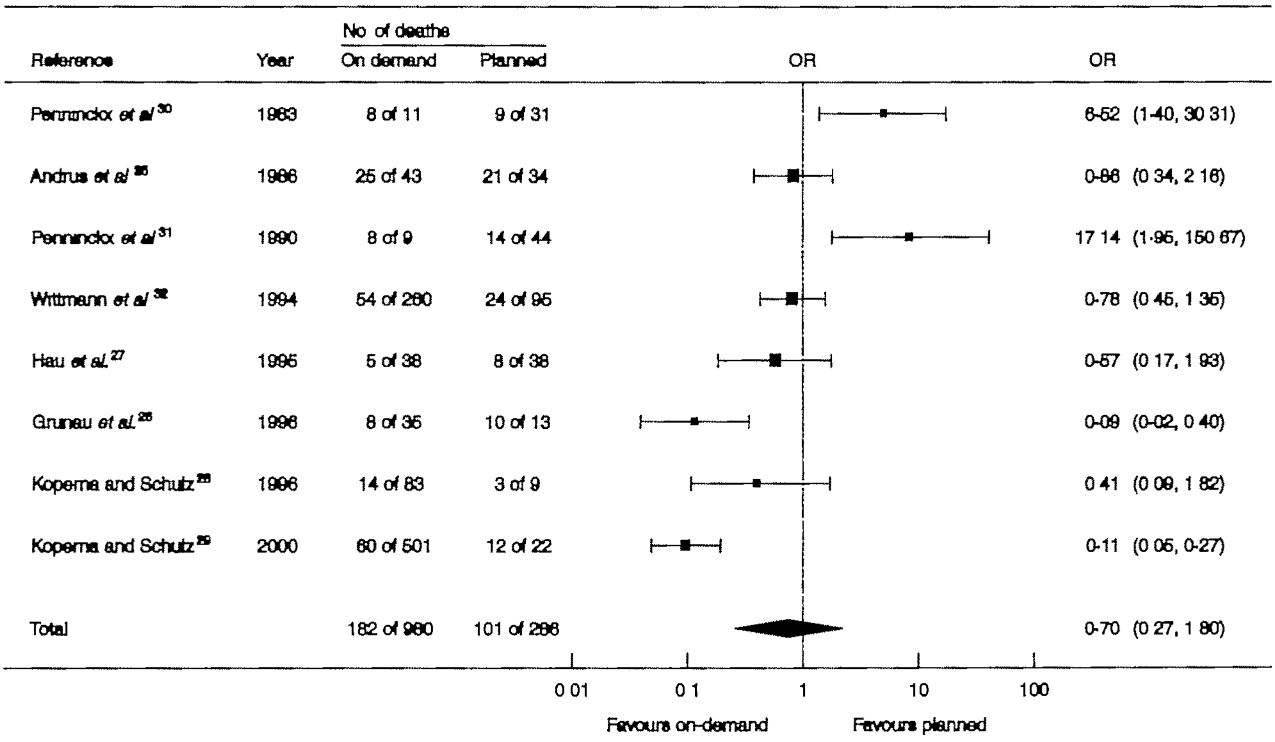
Alternative endpoints

Available data on secondary outcome measures in the individual studies were scarce. Only for alternative endpoints such as the multiple organ failure (MOF), infectious complications, number of relaparotomies, duration of mechanical ventilation, intensive care unit stay and hospital stay could some data be extracted. Both Penninckx *et al.*[30] and Wittmann *et al.*[32] found a lower mortality rate for patients with MOF in the planned relaparotomy group than in the relaparotomy on demand group. Hau *et al.*[27] described a significantly lower incidence of MOF in the on-demand group than in the planned group (24 *versus* 50 per cent respectively; P = 0·01), as well as fewer infectious complications in the on-demand strategy group (40 *versus* 69 per cent; P = 0·01). In the planned relaparotomy group there was a mean of 2·9 relaparotomies per patient, and for relaparotomy on demand the mean was 0·5. Data on duration of mechanical ventilation, intensive care unit stay

Table 2 Clinical and design characteristics of individual studies

		Relaparotomy strategy definition		Allocation					
Reference	Patient population	Planned	On demand	Randomized	Timing	Criteria*	Data collection	Adjustment†	Endpoints other than in-hospital mortality
Penninckx *et al.*[30]	Severe generalized peritonitis from colonic or intestinal origin. Excl: appendicitis	Relaparotomy every 2–3 days	Relaparotomy when signs of sepsis reappear	No	At index	No details	Retrospective	Exclusion of subgroups	Multiorgan failure No. of relaparotomies
Andrus *et al.*[25]	Generalized intraperitoneal infection. Excl: appendicitis	Relaparotomy for more than 500 ml fluid in abdomen, until negative culture	Expectantly	No	At index	By surgeon	?Prospective	Stratified analysis	Hospital stay No. of laparotomies
Penninckx *et al.*[31]	Generalized peritonitis of colonic origin	Relaparotomy every 2 days	Relaparotomy when signs of sepsis persist or reappear	No	At index	No details	Retrospective	Exclusion of subgroups	Multiorgan failure No. of relaparotomies
Wittmann *et al.*[32]	Advanced intra-abdominal infection	One or more relaparotomies	No details	No	At index	By institution and clinical criteria provided	Prospective	Statistical model	Multiorgan failure No. of laparotomies
Hau *et al.*[27]	Intra-abdominal infection	Reoperation	No details	No	At index	No details	Secondary prospective	By design: matching	Multiorgan failure
Koperna and Schulz[28]	Secondary bacterial peritonitis. Excl: primary, pancreatic or traumatic peritonitis	Reoperation in less than 48 h	Reoperation for clinical deterioration or failure to improve	No	At index	No details	Prospective	No adjustment	—
Grunau *et al.*[26]	Postoperative intra-abdominal infection	Reoperation every 24–48 h, planned at index operation	No details	No	Unclear	No details	Secondary prospective	No adjustment	—
Koperna and Schulz[29]	Secondary peritonitis	Reoperation in less than 48 h	Reoperation for clinical deterioration or failure to improve	No	At index	Clinical criteria	Retrospective	No adjustment	—

*Description of allocation criteria when the decision was made during the index operation: no details provided (no details); explicitly stated clinical criteria (clinical criteria); by surgeon or institution (if one surgeon or institution employed planned relaparotomy strategy and others on-demand relaparotomy strategy). †To adjust for differences in prognosis at baseline (index operation) the following methods were employed: by design (randomization or matching); during statistical analysis (stratified analysis or modelling technique); exclusion of subgroups; no form of adjustment. Excl, excluded patients



Reference	Year	No of deaths On demand	No of deaths Planned	OR
Penninckx *et al*[30]	1983	8 of 11	9 of 31	6·52 (1·40, 30·31)
Andrus *et al*[25]	1986	25 of 43	21 of 34	0·86 (0·34, 2·16)
Penninckx *et al*[31]	1990	8 of 9	14 of 44	17·14 (1·95, 150·67)
Wittmann *et al*[32]	1994	54 of 280	24 of 95	0·78 (0·45, 1·35)
Hau *et al.*[27]	1995	5 of 38	8 of 38	0·57 (0·17, 1·93)
Grunau *et al.*[26]	1996	8 of 35	10 of 13	0·09 (0·02, 0·40)
Koperna and Schulz[28]	1996	14 of 83	3 of 9	0·41 (0·09, 1·82)
Koperna and Schulz[29]	2000	60 of 501	12 of 22	0·11 (0·05, 0·27)
Total		182 of 980	101 of 286	0·70 (0·27, 1·80)

Fig. 2 Individual and pooled odds ratios (ORs) (planned *versus* on-demand relaparotomy) for the eight studies. Pooling was according to the random-effects model. Squares and bars indicate study size and confidence interval, respectively. Elongated diamond represents the confidence interval of 0·27, 1·80. Test for heterogeneity of the eight studies: $\chi^2 = 40.7$, d.f. = 7, $P < 0.001$; test for overall effect: $P = 0.5$

and infectious complications were provided in insufficient detail for comparison of the two treatment strategies; one study[25] described a shorter median(s.d.) hospital stay for relaparotomy on demand than for planned relaparotomy (38(25) *versus* 46(38) days respectively).

Discussion

This meta-analysis showed that the pooled OR of in-hospital mortality is in favour of patients with secondary peritonitis treated by the relaparotomy on demand strategy. However, this apparent advantage over the planned strategy was not statistically significant because of the heterogeneity of the studies. Stratified analysis showed that the combined OR for the prospective studies, as well as for the studies published from 1995 onwards, was significantly in favour of the on-demand strategy, albeit in a subgroup analysis.

Meta-analysis of observational studies is a method of assessing the efficacy of a particular treatment. As opposed to randomized clinical trials, the methodological design of observational studies lacks randomization, resulting in heterogeneity of patient population, design and outcome[11,33]. In such circumstances the effects of confounding and publication bias must be attended to when performing any meta-analysis[34,35]. A non-randomized allocation of patients implies that surgeons prefer a treatment strategy because they believe a certain patient needs a particular treatment, thereby mixing prognosis with treatment decisions. The amount of evidence generated by the available studies was limited because of their small size, their non-randomized allocation, and the substantial differences between studies in the components of the on-demand strategy. Because of the non-randomized allocation, there is a high risk that treatment decisions are related to prognosis (confounding by indication)[36,37]. Statistical adjustment for important prognostic factors requires sufficiently large studies and sufficiently detailed publication of data. In general, the eight available studies lacked the details needed to perform such an adjustment.

The χ^2 test showed a significant heterogeneity between the included studies; variations in study design, allocation of the intervention, and definition of treatment strategy used lead to potential heterogeneity. Analysis of patient characteristics showed that only for the severity of disease, as expressed by various scoring systems, was there a possible disadvantage for patients in the planned relaparotomy groups. Other patient characteristics were equally distributed between the groups, but it must be emphasized that lack of data within the individual studies made sufficient retrieval for cumulative analysis difficult. The random-effects model was deployed to correct for heterogeneity in order to calculate the pooled OR. This model assumes a different underlying effect for each study, taking this into account as an additional source of variation[38]. Calculation of the pooled OR using the fixed-effects model in such cases would result in an artificially narrow 95 per cent confidence interval, whereas the random-effects model gives a more realistic confidence interval.

Nine studies containing potentially useful data on either the planned relaparotomy or the on-demand relaparotomy strategy were omitted from the meta-analysis because they addressed only one treatment strategy. Separate analysis of these studies showed a median (range) mortality rate of 29 (23–44) per cent for the eight studies addressing the planned strategy[1,6,18–23] and a 14 per cent mortality rate for the study addressing the on-demand strategy[24]. Formally, these studies were not part of the meta-analysis and caution should be used in drawing conclusions from these mortality rates. Uniformity of patient groups, study design, treatment and potential adverse outcome were not taken into account.

There is an evident lack of sensitivity and specificity of Medline searches in general, potentially causing selection bias[39]. To reduce this lacuna in the present search of the literature, a systematic search was performed, retrieving multiple-language articles, and a cross-reference search of eligible publications was undertaken. It is known that studies with negative results are less likely to be published[35,40] and, as a consequence, actual differences in surgical treatment strategies for peritonitis may be smaller than that calculated by accumulation of published data. In the analysis of the included studies, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was used. This is the observational meta-analysis equivalent of the QUality Of Reporting Of Meta-analyses (QUOROM) statement of randomized clinical trials, and provides authors with a guideline for reporting the results of such analysis in the hope of improving quality[11,41].

It must be remembered that the studies available here for meta-analysis are of relatively low methodological quality, consisting of level II–IV evidence. This mirrors the reality that the surgical management of secondary peritonitis is founded on low-level evidence. This is emphasized by the lack of detailed data on alternative endpoints in the individual studies. The present meta-analysis reviews the best available evidence. Decision-making on both in the planned relaparotomy and relaparotomy on demand policies in patients with secondary peritonitis remains non-evidence-based and dependent largely on a 'gut feeling'. A planned relaparotomy strategy is frequently employed when the source of infection is not eliminated at the time of the index operation, or in the face of types of contamination or aetiological factors such as faecal soiling or ischaemia. In the relaparotomy on demand strategy, deterioration or lack of improvement is monitored by observing clinical variables, quantitative measurement of changes in organ function, and contrast-enhanced computed tomography (CT). When adhering to the more conservative on-demand strategy, frequent CT imaging to explore the possibility of percutaneous intervention and to direct surgical reintervention may be beneficial[42,43]. Furthermore, the success of the on-demand policy may depend largely on the strict definition and validation of relaparotomy criteria.

In the search for studies comparing the planned and on-demand relaparotomy strategies, no randomized clinical trial was retrieved, although a separate search for review articles on relaparotomy in abdominal sepsis[2,4,5,8,22,44–64] revealed numerous studies that have long emphasized the need for such a trial[8,59,65,66]. There is a great need for a well designed, sufficiently large, randomized trial involving clearly defined patient groups to resolve the uncertainty about the best surgical strategy in patients with abdominal sepsis. Such a multicentre randomized study is currently being carried out in The Netherlands.

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CHANGE OF PUBLISHER

From volume 90, issue 1, January 2003, the *British Journal of Surgery* will be published by John Wiley & Sons Ltd.

Therefore from **Monday 9 September 2002** all papers and correspondence should be sent to:

The Editor, *BJS*, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester PO19 8SQ, UK. Telephone: + 44 (0) 1243 779777. Facsimile: + 44 (0) 1243 775878.

Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival

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Background: The results of surgical treatment for intrahepatic cholangiocarcinoma (ICC) and specific factors influencing survival are still unclear.
Methods: Between 1984 and 2001, 62 patients with ICC underwent laparotomy, with a 77 per cent (48 patients) resectability rate. The tumours in these 48 patients were reviewed retrospectively to examine the relationship between gross appearance (mass forming, periductal infiltrating, intraductal growth, and mass forming plus periductal infiltrating) and patient survival, as well as the manner of recurrence. In patients with mass-forming and mass-forming plus periductal infiltrating types, univariate and multivariate analyses of potential prognostic factors were performed.
Results: The 1-, 3- and 5-year survival rates were 62, 38 and 23 per cent respectively. All patients with the intraductal growth type remained alive after intervals ranging from 8 to 72 months. Univariate analysis showed multiple hepatic lesions, liver capsule invasion, presence of cancer cells in the resection margin, and high serum carbohydrate antigen (CA) 19-9 level to be significant negative prognostic factors. Lymph node involvement, however, was not identified as a significant prognostic factor. With multivariate analysis, multiple hepatic lesions and high serum CA19-9 concentration were found to be significantly related to prognosis. The most frequent recurrence site was the remnant liver.
Conclusion: These results suggest that the intraductal growth type of tumour should be treated as a distinct entity compared with other types of ICC. Multiple tumours and high serum CA19-9 level were signs of dismal prognosis, whereas not all patients with lymph node involvement had a poor prognosis.

Paper accepted 17 July 2002

British Journal of Surgery 2002, **89**, 1525–1531

Introduction

Intrahepatic cholangiocarcinoma (ICC) is relatively rare, despite being the second most common primary hepatic tumour after hepatocellular carcinoma. It has been reported to comprise only 5–10 per cent of primary liver neoplasms[1,2]. The prognosis of patients with ICC is generally poor[3,4], although aggressive surgical treatment seems to afford hope for long-term survival in some cases[5–7].

To determine the benefits and limits of current surgical resection for ICC, knowledge of the factors that influence survival after operation may be important. Until now, there have been several reports on analysis of surgical treatment of ICC, most with a small numbers of cases[2,6,8–14]. Because of the rarity of the tumour and the low resectability rates, few studies have reported results from a large number of patients undergoing surgical resection in a single institution[5,15–17]. The recent development of surgical techniques in hepatobiliary surgery, however, has made it possible to apply aggressive surgical approaches for ICC, improving the resectability rate. The present study evaluated the results of surgical resection obtained from a relatively large number of patients with ICC, and studied several prognostic factors affecting patient survival, including lymph node involvement, which has been reported as one of the strongest prognostic factors[2,4,10–13,15,16].

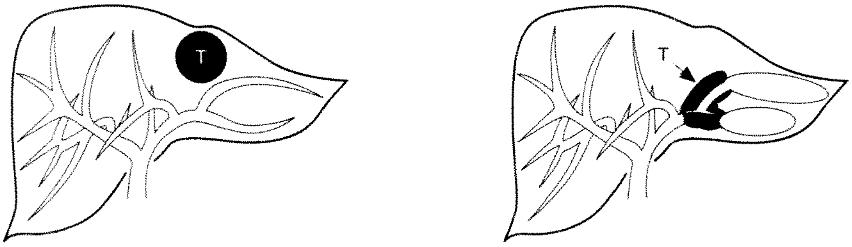
Patients and methods

Between December 1984 and September 2001, 62 patients with ICC were treated surgically at the Chiba University

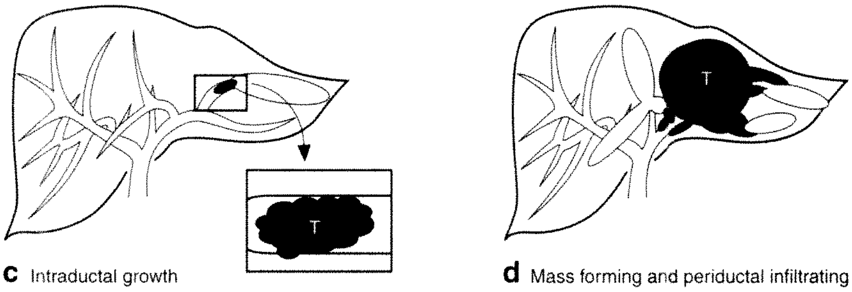
The Editors have satisfied themselves that all authors have contributed significantly to this publication

Hospital. ICC was defined as malignancy arising from the intrahepatic bile duct; perihilar (Klatskin) tumours were excluded. There were 37 men and 25 women, with a mean age of 64 (range 30–81) years. Among the 62 patients, 14 underwent palliative resection or exploratory laparotomy only (palliative treatment group), because they were found to have peritoneal dissemination, extensive invasion along Glisson's capsule, multiple liver metastases or extensive lymph node metastases at the time of operation. Palliative resection was defined as macroscopically incomplete resection in which parts of the tumour could not be resected. In the remaining 48 patients (the resection group), surgical resection with macroscopically curative intent was possible (resectability rate 77 per cent). Hepatic resection was the basic operative procedure for this type of carcinoma, and the extent of hepatic resection was as follows: 26 extended hemihepatectomies (including four trisegmentectomies), 11 hemihepatectomies, one central hepatectomy (Couinaud segments[18] IV, V and VIII), nine segmentectomies and one subsegmentectomy. Extrahepatic bile duct resection, which was performed when the tumour was judged to have invaded the bile duct or metastasized the lymph node within the hepatoduodenal ligament, was combined with various types of hepatectomy in 26 patients. Resection and reconstruction of the portal vein (seven patients), inferior vena cava (three), portal vein and hepatic artery (one), and portal vein and inferior vena cava (one) was also performed when the cancer was judged to have invaded these vessels. Lymph node dissection, including at least the area of the hepatoduodenal ligament (regional lymph node defined by the Union Internacional Contra la Cancrum (UICC)[19]), was completed in 35 patients. A small number of patients had postoperative adjuvant chemotherapy. Chemotherapy via hepatic artery infusion was given to six patients. No chemotherapy was given to other patients until the detection of recurrence. Postoperative radiotherapy was not performed in any patient. All patients, except those who died in hospital, were followed closely at the institution's outpatient clinic with periodic examinations of tumour markers, ultrasonography, computed tomography and/or radioisotope scintigraphy. The median length of follow-up was 70·8 months.

Pathological examination was performed on all resected specimens, which were re-examined for the purposes of the study by a single pathologist. Gross appearance of the cut surface of ICCs was categorized into the following types according to the classification proposed by the Liver Cancer Study Group of Japan: mass forming (MF), periductal infiltrating (PI), intraductal growth (IG), and other[20]. The MF type was characterized by the presence of a round-shaped mass in the liver parenchyma with a distinct border, the PI type by tumour infiltration along the bile duct, and the IG type by papillary and/or granular growth within the bile duct lumen (*Fig. 1*). When more than one type was



a Mass forming **b** Periductal infiltrating



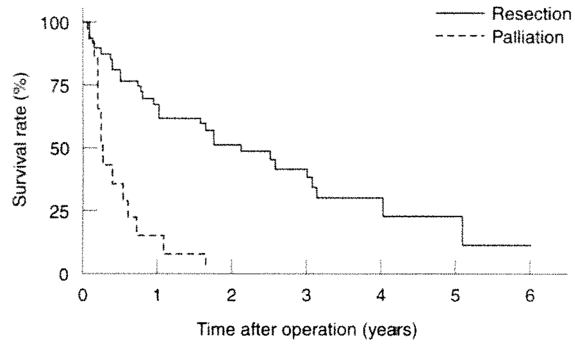
c Intraductal growth **d** Mass forming and periductal infiltrating

Fig. 1 Gross appearance of intrahepatic cholangiocarcinoma according to the classification proposed by the Liver Cancer Study Group of Japan[20]. **a**, Mass-forming type; **b**, periductal infiltrating type; **c**, intraductal growth type; **d**, mass-forming plus periductal infiltrating type. T, tumour

found, all of the types involved were recorded, in order of the degree of involvement; the first recorded type was the predominant type, for example 'MF + PI type' (*Fig. 1*). Resected specimens were also examined for several parameters that were used for further analysis of potential prognostic factors, as described below. Tumour stage was defined according to the pathological tumour node metastasis (pTNM) classification proposed by the UICC[19].

The relationship between gross appearance and patient survival was investigated first. The manner of recurrence was also studied, according to respective types. Recurrence was detected by means of imaging, tumour markers and/or histopathological examination. In patients with predominantly MF type (MF and MF + PI types), clinicopathological features were analysed as variables possibly affecting prognosis. These variables included age of patients, preoperative serum carbohydrate antigen (CA) 19-9 level, location of main tumour, size of principal tumour, tumour number, liver capsule invasion, histological tumour differentiation, microscopic vessel (vascular or lymphatic) invasion, perineural invasion, pTNM stage, presence of cancer cells in the resection margin and lymph node involvement. These were all tumour-related factors, and variables related simply to the operative procedure, such as combined lymph node dissection and combined vascular resection and reconstruction, were not included. In four patients the preoperative CA19-9 level had not been determined. Similarly, size of tumour, microscopic vessel invasion and perineural invasion were not available for one patient, because his specimen had not been preserved completely.

The cumulative survival rates were calculated with the Kaplan–Meier method, and differences in univariate survival were examined using the log rank test. The Cox proportional hazards model was employed for multivariate regression analysis. $P < 0\cdot05$ was considered statistically significant.



No. at risk						
Resection	48	24	19	10	4	2
Palliation	14	2	0	0	0	0

Fig. 2 Actuarial survival of patients with intrahepatic cholangiocarcinoma according to resectability. $P < 0\cdot001$ (log rank test)

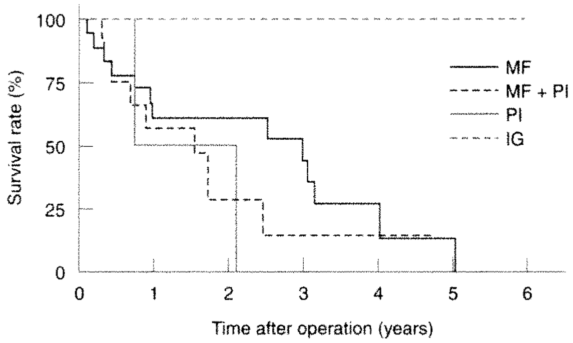
Results

Overall survival

There were four in-hospital deaths (8 per cent) after hepatic resection. Median survival time was 25·5 (range 0·3–72) months for patients in the resection group, including in-hospital deaths. The 1-, 2-, 3-, 4- and 5-year survival rates were 62, 51, 38, 30 and 23 per cent respectively (*Fig 2*). Two patients survived for more than 5 years. Comparative survival in the resection group *versus* the palliative treatment group is shown in *Fig. 2*. Significantly better median survival was achieved in patients having resection than in those receiving palliation (25·5 *versus* 2·3 months; $P < 0\cdot001$). No patient in the palliative treatment group lived for more than 2 years.

Gross appearance and patient survival

Of 48 patients in the resection group, 21 (44 per cent) had the MF type of ICC, 15 (31 per cent) had the MF + PI type, nine (19 per cent) had the IG type and two (4 per cent) had the PI type. In one patient gross appearance could not be classified, because all three types were equally and complexly mixed. This patient was excluded from further



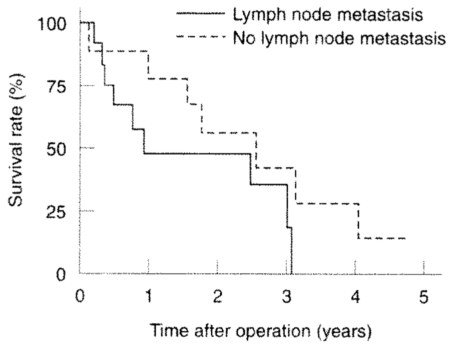
No. at risk						
MF	19	10	10	5	2	1
MF + PI	13	6	3	1	1	0
PI	2	1	1	0	0	0
IG	9	6	5	4	1	1

Fig. 3 Actuarial survival after surgical resection of intrahepatic cholangiocarcinoma, according to gross appearance of the primary tumour. MF, mass forming; PI, periductal infiltrating; IG, intraductal growth. $P < 0\cdot005$ (IG *versus* all other types, log rank test)

Table 1 Sites of first recurrence after surgical resection for intrahepatic cholangiocarcinoma

			Site of first recurrence				
Gross appearance	No. of patients	No. of recurrences	Liver	Lymph node	Peritoneum	Bile duct	Remote organ
Mass forming	21	16	11	1	1	0	3
Mass forming + periductal infiltration	15	11*	4	4	1	1	0
Periductal infiltration	2	2	0	2	0	0	0
Intraductal growth	9	1	0	0	0	0	1
Total	47	30	15	7	2	1	4

*Includes one patient in whom the recurrence site was not well clarified



No. at risk					
Lymph node metastasis	9	7	5	3	2
No lymph node metastasis	14	5	5	1	0

Fig. 4 Actuarial survival after surgical resection of predominantly mass-forming type of intrahepatic cholangiocarcinoma, according to nodal status in patients in whom lymph node dissection was performed

analysis. *Fig. 3* shows comparative survival by the gross appearance among patients in the resection group, excluding those who died in hospital. Two patients with in-hospital death had the MF type and others had the MF + PI type. Eight of nine patients with the IG type were still alive 8–72 months after operation, with no recurrence. Another patient is still alive 26 months after operation, although he had tumour recurrence in the lung. In comparison with the IG type, patients with the MF, MF + PI and PI types had a much worse prognosis. The difference in survival rates between MF and MF + PI types was not significant.

Modes of recurrence

Recurrence occurred in 30 patients. The sites of first recurrence are shown in *Table 1*. The most common site of recurrence was the remaining liver. This was seen most frequently in patients with the MF type (11 of 16 patients with recurrence), while recurrence in the lymph nodes was also seen with relative high frequency in patients with the MF + PI and the PI types. In MF and MF + PI types, patients with multiple tumours tended to have recurrence in the remaining liver (seven of ten patients with recurrence who had multiple tumours at operation).

Analysis of prognostic factors

Patients with IG and PI types were excluded from the study, because, as mentioned above, those with the IG type have an extremely favourable prognosis compared with those with predominantly MF types (MF and MF + PI), and the number of patients with the PI type was too small for analysis.

Univariate analysis of predominantly mass-forming types

Of 12 variables, univariate analysis showed that multiple hepatic lesions, liver capsule invasion, presence of cancer cells in the resection margin and high CA19-9 level (greater than 1000 units/l, which was the critical level for patient survival) were significant negative prognostic factors for overall patient survival. Age, location of tumour, size of principal tumour, histological tumour differentiation, microscopic vessel invasion, perineural invasion and pTNM stage did not influence survival. Lymph node involvement was not identified as a significant prognostic factor in patients who underwent lymph node dissection (*Fig. 4*). Three patients with lymph node involvement survived for more than 3 years after surgical resection.

Multivariate analysis of predominantly mass-forming types

The four significant prognostic factors determined by univariate analysis were included in a subsequent multi-

Table 2 Multivariate analysis of prognostic factors in patients with a predominantly mass-forming type of intrahepatic cholangiocarcinoma

Prognostic factor	Relative risk	*P*
Preoperative CA19-9 level (> 1000 units/l)	5·42 (1·48, 19·84)	0·011
Tumour number (multiple)	3·90 (1·14, 13·34)	0·030
Liver capsule invasion (positive)	3·94 (0·89, 17·56)	0·072
Resection margin (positive cancer cells)	1·47 (0·40, 5·36)	0·56

Values in parentheses are 95 per cent confidence intervals. CA, carbohydrate antigen

variate analysis. This analysis revealed multiple hepatic lesions and high serum CA19-9 level to be independently associated with a poor prognosis (*Table 2*).

Discussion

Although surgical resection was shown to provide a chance of long-term survival for patients with ICC in this study and in others[5–7], the prognosis after aggressive resection remains unsatisfactory. The 5-year survival rate is reportedly approximately 25 per cent, which was similar to the results in the present series (23 per cent).

In 1997, the Liver Cancer Study Group of Japan proposed a gross classification of ICC based on the macroscopic appearance of the cut surface of the tumour into MF, PI and IG types[20]. Several authors have reported that these macroscopic types are associated with their biological behaviour[17,21–27]. Among the three types, patients with the IG type seemed to have the best outcome after tumour resection, although there have been only a few scattered reports. Isaji *et al.*[22] reported that all of three patients with the IG type were still alive after 26–138 months without recurrence. Isa *et al.*[12] described one patient with the IG type who survived for 98 months without recurrence, despite positive lymph node involvement at the time of operation. Itamoto *et al.*[24] also reported one patient with the IG type who survived for 133 months without recurrence. In a study by Suh *et al.*[28], 13 of 16 patients were still alive after 12–160 months without recurrence, and two patients were also alive 27 and 44 months after operation, with recurrence. In the present study, all nine patients with the IG type remained alive for periods ranging from 8 to 72 months: eight patients without recurrence and one with recurrence. These results indicate that patients with the IG type might strongly expect a favourable prognosis after surgical resection, and rarely have tumour recurrence after surgical resection. The majority of previous reports in which surgical results were analysed may include this type of ICC, making relevant interpretation of these analyses difficult. The IG type of ICC might have special biological characteristics, and therefore this type of tumour should be treated as an entity distinct from other types of ICC. With regard to other types of ICC, the differences in survival rates among respective types were not significant.

In contrast to the IG type, the prognosis for predominantly MF types of ICC was particularly unfavourable, although there were some long-term survivors. The univariate analysis revealed a poorer prognosis for patients with multiple hepatic lesions, liver capsule invasion, presence of cancer cells on resection margin, and a high serum CA19-9 level. Several of these findings were consistent with those of other previous reports[2,6,8–10,15], but lymph node involvement, which is usually shown to be strongly associated with poor outcome[2,4,10–13,15,16], did not predict poor survival in the present series. Multivariate analysis showed that high serum CA19-9 concentration and multiple tumours were independently significant prognostic factors. Although it is possible that multiple tumours resulted from multicentric development, a histological similarity among all tumours, which generally consisted of one large tumour with smaller-sized lesions, strongly suggested that these tumours were one principal nodule and intrahepatic metastases. Similar to hepatocellular carcinoma, ICC containing a mass-forming structure seems to have a tendency to spread via the portal vein system, as there was a close relationship between intrahepatic metastases and portal venous invasion in the autopsy series[29]. Although all patients in the present series underwent anatomical hepatic resection on the basis of this fact, the study revealed that the most frequent recurrence site was the remaining liver in the predominantly MF types of ICC. These results suggest that the existence of multiple tumours may be a strong indication of dispersed metastases in the liver, resulting in a poor prognosis.

Most previous series have shown that one of the strongest prognostic factors is lymph node involvement[2,4,10–13,15,16]. All of these studies reported that no patients with lymph node involvement survived for more than 3 years after operation. Inoue *et al.*[16] insisted that lymph node metastasis in the MF type of ICC is a sign of non-curative disseminated disease, and therefore that hepatectomy is contraindicated if metastatic involvement is observed at the time of lymph node sampling. On the other hand, Murakami *et al.*[30] and Weber *et al.*[8] reported long-term survivors (more than 5 years) with lymph node metastasis. In the present series there were three patients with lymph node involvement who lived for more than 3 years after resection. These results suggest that, although lymph node involvement may generally be associated with an unfavourable prognosis, long-term survival might be expected following aggressive surgical resection, including lymph node dissection, in highly selected patients with nodal metastasis. As suggested by others[30], some types of ICC, even those with nodal spread, might have less aggressive and slower-growing characteristics. Further studies are required to be able to select patients with such types of tumour, and further prospective studies should be undertaken to clarify the significance of lymph node dissection for patient survival.

This study has shown that, even after curative resection, the majority of patients, except those with the IG type of ICC, experienced recurrence. However, there have been few reports concerning treatment for recurrence[8,31]. This might be because there are no effective non-surgical therapeutic modalities at present. The benefits of adjuvant chemotherapy and/or radiation therapy remain unproven. Only surgical approaches for treatment of ICC recurrence have been reported to be effective[31]. Unfortunately, however, a large proportion of patients had recurrences that were beyond the scope of surgical treatment. Therefore, the development of effective adjuvant treatment protocols is needed.

Total hepatectomy and subsequent liver transplantation had been considered as one option for the treatment of patients with greatly advanced ICC or recurrent tumour following initial resection. However, owing to a high rate of recurrence and generally poor survival[15,32,33], it is doubtful whether transplantation is justified at present for patients with ICC. Only a highly selected group of patients with early tumour stage may potentially benefit from liver transplantation[7,10].

In conclusion, because patients with the IG type of ICC may have an extremely favourable prognosis after surgical resection, this type of tumour should be treated as an entity distinct from other types of ICC. Multiple tumours and high serum CA19-9 levels were signs of dismal prognosis, and not all patients with lymph node involvement had a poor prognosis.

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Original article

A 10-year experience of complex liver trauma

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Background: Liver trauma is a relatively rare surgical emergency but mortality and morbidity rates remain significant. It is likely that surgeons outside specialist centres will have limited experience in its management; therefore best practice should be identified and a specialist approach developed.
Methods: Data collected from 52 consecutive patients over a 10-year interval were examined to identify best practice in the management of these injuries.
Results: The majority of injuries occurred as a result of road traffic accidents; 39 (75 per cent) of the 52 patients were stable at presentation to the referring hospital. In 36 patients (69 per cent) the liver injury was a component of multiple trauma. Ultrasonography, computed tomography or no radiological investigation was used in the referring hospital in 18 (35 per cent), 25 (48 per cent) and nine (17 per cent) patients respectively. Operative management was undertaken in the referring hospital in 26 patients (50 per cent). The overall mortality rate was 23 per cent (12 of 52 patients), and increased with increasing grade of severity. Eight of 26 patients managed surgically at the referring hospital died, compared with four of the 26 patients managed without operation (*P* not significant). The median time from arrival at the referring hospital to operation was 4 h for haemodynamically stable patients and 3 h for those who were haemodynamically unstable.
Conclusion: Most patients with liver trauma can be managed conservatively. Operative management carried out in non-specialized units is associated with high mortality and morbidity rates. Abdominal injuries should raise a high index of suspicion of liver injury, and the data suggest that computed tomography of the abdomen should precede laparotomy (even in some haemodynamically unstable patients) to facilitate discussion with a specialist unit at the earliest opportunity.

Paper accepted 15 July 2002

British Journal of Surgery 2002, **89**, 1532–1537

Introduction

Blunt and penetrating injuries to the liver are a comparatively rare surgical emergency in the UK. Minimal exposure of the emergency on-call general surgeon to these injuries may necessitate the development of a specialist approach and, where possible, management in specialist centres[1].

The liver is frequently injured following abdominal trauma and associated injuries contribute significantly to mortality and morbidity, and may cause the liver injury to be masked and diagnosis delayed[2]. In recent years the treatment of abdominal injuries has evolved and a non-operative approach has been adopted in an increasing number of selected patients[3]. Mortality rates from complex liver trauma still remain high despite improvements in resuscitation, anaesthesia and intensive care facilities[1].

Patients with suspected liver injuries should be managed in accordance with the protocols of the Advanced Trauma Life Support (ATLS) of the American College of Surgeons' Committee on Trauma. Following the primary survey, a high index of suspicion should be raised by the presence of external evidence of abdominal injury, abdominal pain and, particularly, right upper quadrant tenderness[4].

Diagnosis of hepatic injury can be facilitated by ultrasonography and computed tomography (CT) of the abdomen. Ultrasonography has gained increased acceptance, particularly in the emergency department, and proponents suggest that the advantages are portability of the equipment and a high sensitivity, specificity and accuracy at detecting haemoperitoneum[5–7]. CT has a higher sensitivity than ultrasonography in detecting hepatic injury, and also in identifying intestinal injuries and retroperitoneal organ injury[8–10]. The two investigations, however, should be seen as useful adjuncts to one another both for initial assessment and in the ongoing evaluation of patients[5].

In the shocked or haemodynamically unstable patient, ATLS protocols suggest that the patient should undergo immediate laparotomy[4]. It has recently been suggested that patients who are haemodynamically stable after resuscitation, requiring no more than 4 units of blood, with haemoperitoneum no greater than 500 ml or simple parenchymal laceration or haematoma on CT can be managed without operation. This study reviewed the management and outcome of patients referred from district general hospitals (DGHs)[11].

Patients and methods

Data from all patients referred to the authors' unit from March 1991 to March 2001 were collected and analysed retrospectively. The mechanisms of injury, initial management, delays occurring after arrival at the presenting hospital, and treatment and consequent management were analysed. Liver trauma was classified using the organ injury scale of the American Association for the Surgery of Trauma[12].

In accordance with the current ATLS protocols, in which immediate laparotomy is recommended for patients who have sustained abdominal trauma and who are haemodynamically unstable, patients were divided into two main groups: those who were haemodynamically stable at presentation and those who were haemodynamically unstable[4]. Haemodynamic stability was defined as a systolic blood pressure greater than 100 mmHg and pulse rate lower than 100 beats per minute at the time of presentation to the referring hospital.

Data were collected on the presence of coexisting injuries at the time of presentation. These were divided broadly into head, neck and spinal, other abdominal and pelvic injury (including splenic injury and visceral perforation), chest injury (including rib fracture, haemothorax or pneumothorax, lung and cardiac contusion), peripheral injury (including long bone fractures) and a final group in which there were no other significant injuries.

All statistical analyses were carried out with the Instat® (Graphpad Software, San Diego, California, USA) computer program using Fisher's exact test and the χ^2 test where appropriate. Statistical significance was set at $P < 0{\cdot}05$.

Results

Over the 10-year period, 52 patients (26 males and 26 females) were referred to the authors' unit for management of liver trauma. Liver trauma from road traffic accidents accounted for 67 per cent of all injuries (35 patients); falls, assaults and crush injuries were responsible for 13, 12 and 8 per cent respectively. There were no statistically significant relationships between mechanisms of injury and either grade of liver injury or presence of haemodynamic stability, and 40 (77 per cent) of the 52 patients were haemodynamically stable at presentation to the referring hospital, with no difference observed between grades of liver trauma.

Liver injury occurred as a component of multiple trauma in 36 patients (69 per cent). Other abdominal and chest injuries were the commonest coexisting injuries, with ten patients (19 per cent) suffering other abdominal injuries and 21 (40 per cent) having chest injuries. There was no relationship between the grade of trauma and the frequency of coexisting injury for either haemodynamically stable or unstable patients. There was also no significant relationship between haemodynamic stability and either the presence or number of coexisting injuries or the grade of liver trauma.

The numbers of patients in the haemodynamically stable and unstable groups who underwent ultrasonography, CT or no imaging at the referring hospital are shown in *Table 1*. Of the 40 haemodynamically stable patients, 23 underwent CT compared with two of the 12 patients in the unstable group ($P < 0{\cdot}02$, Fisher's exact test), and 14 haemodynamically stable patients had abdominal ultrasonography compared with four in the unstable group (P not significant). Of the nine patients who did not have imaging at the referring hospital, three were haemodynamically stable and six were haemodynamically unstable (P not significant) (*Table 1*). In patients who were not imaged, the use of diagnostic peritoneal lavage was not recorded.

Half ($n = 26$) of all patients were managed surgically at the referring hospital, and of these 17 were haemodynamically stable. In the conservatively managed group ($n = 26$), 23 patients were haemodynamically stable. There was no

Table 1 Liver injury scale and use of diagnostic radiology in 52 patients

Liver injury scale	Ultrasonography	Computed tomography	No imaging
I			
Stable	0	0	0
Unstable	0	0	0
II			
Stable	4	5	0
Unstable	1	0	2
III			
Stable	2	14	0
Unstable	1	1	1
IV			
Stable	1	1	2
Unstable	1	0	1
V			
Stable	7	3	1
Unstable	0	1	2
VI			
Stable	0	0	0
Unstable	1	0	0
Total	18 (35)	25 (48)	9 (17)

Table 2 Liver injury scale and primary management in 52 patients

	Primary management		
Liver injury scale	Conservative	Operative	Total
I			
Stable	0	0	0
Unstable	0	0	0
II			
Stable	6	4	10
Unstable	0	2	2
III			
Stable	11	4	15
Unstable	2	2	4
IV			
Stable	3	0	3
Unstable	0	3	3
V			
Stable	4	8	12
Unstable	0	2	2
VI			
Stable	0	0	0
Unstable	0	1	1
Total	26 (50)	26 (50)	52 (100)

statistically significant relationship between the primary management and the grade of liver trauma, although 14 patients with a liver injury score of IV or greater were treated surgically (*Table 2*). Twenty-six patients underwent surgical procedures as part of the primary treatment; 15 of these were treated with packing of the liver alone, four had haemostatic sutures in addition to packing, and five underwent emergency splenectomy at laparotomy in addition to treatment of the liver injury. There was no statistically significant relationship between the primary treatment and the presence of coexisting injuries, although twice as many patients with other abdominal injuries were treated surgically than were managed conservatively.

Data were available on the time taken from arrival at the primary hospital to the commencement of operation at that hospital in 22 of the 26 patients managed surgically. In patients who were haemodynamically stable the median time to operation was 4 h (range from 1 h to 4 days), and in those who were haemodynamically unstable the median was 3 (range 1–8) h (P not significant).

There were five main groups of complication: (1) renal failure, (2) infection or sepsis, (3) biliary or pancreatic leakage or fistulas, (4) adult respiratory distress syndrome and (5) death. The overall mortality rate in the series was 23 per cent (12 of 52 patients), and the mortality rate increased as the severity of the grade of hepatic injury increased: grade II, one of 12 patients died; grade III, three of 19 patients; grade IV, two of six patients; grade V, five of 14 patients; and the only patient with grade VI injury died (P not significant). The morbidity rate also increased as the grade of injury increased, rising from two of 12 patients with grade II injuries to nine of 14 with grade V injuries (P not significant). There was no significant correlation between the presence or absence of coexisting injuries and mortality or morbidity rate, but both rates were higher in patients who had sustained other abdominal ($n = 10$) or chest ($n = 21$) injuries (mortality: five of ten patients and seven of 21 respectively; morbidity: two of ten patients and four of 21), compared with death in one of 16 patients ($P < 0{\cdot}04$ *versus* other abdominal or chest injuries, Fisher's exact test) and morbidity in three patients with liver injury in isolation.

Ultrasonography was performed in 18 (35 per cent) of the 52 patients at the referring hospital, with 14 of these being haemodynamically stable and 15 being managed surgically. CT was carried out in 25 patients (48 per cent), 23 of whom were haemodynamically stable with only three being managed surgically. Of nine patients (17 per cent) who had no radiological investigation performed, three were haemodynamically stable and eight were managed surgically ($P < 0{\cdot}001$, operative *versus* non-operative by whether radiology performed, χ^2 test). In the group of 12 unstable patients, six were managed surgically without investigation, four had ultrasonography before operation, and two had CT and were managed conservatively (*Fig. 1*) ($P < 0{\cdot}01$, operative *versus* non-operative by whether radiology performed, χ^2 test). Of the 26 patients who underwent operation as the primary treatment, eight died and 14 suffered morbidity, almost double the rates in the 26 patients who were managed without operation (mortality, four patients; morbidity, eight patients) (P not significant).

Following transfer to the referral centre, 28 patients were managed surgically. Fourteen patients had an anatomical resection and six returned to theatre for pack removal alone. Two patients returned to theatre for repacking, three for hepatic vein repairs, and one each for repair of a bile duct injury, evacuation of a haematoma and a caval embolectomy. There was no significant relationship between the grade of liver trauma and the management of liver injury. However, the frequency of further surgical procedures increased with increasing liver injury grade. Five of 12 patients with grade II injury, seven of 19 with grade III, three of six with grade IV, and 12 of 14 with grade V injury required a further operation. In the group of 26 patients treated surgically at the primary hospital, 22 had a further procedure at the referral centre, but only six of the 26 patients managed conservatively at the primary hospital required subsequent operations ($P < 0{\cdot}001$, χ^2 test).

Eight of the 26 patients operated on at the referral centre died and 16 patients suffered morbidity, whereas four of the 26 patients managed conservatively died and six had

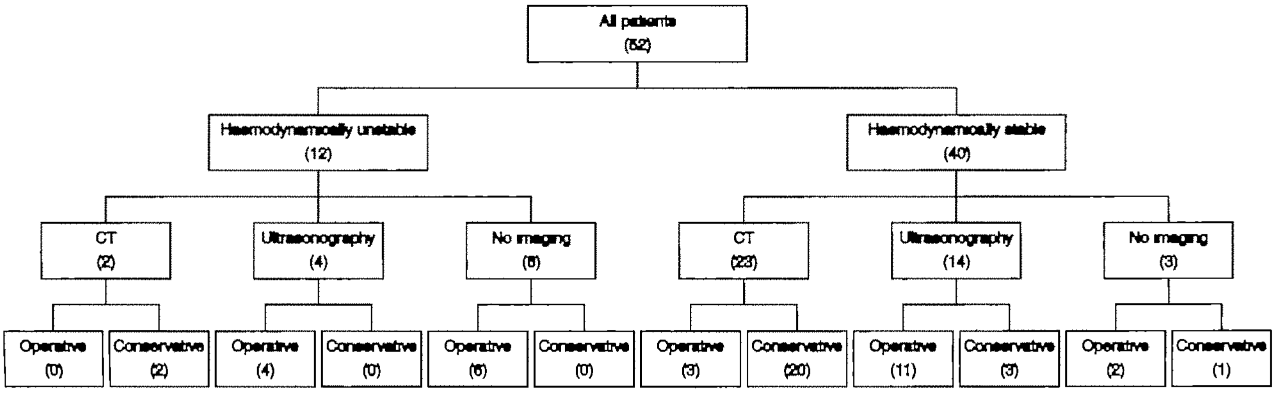

Fig. 1 Diagnostic imaging performed in 52 patients admitted to district general hospitals with liver trauma. CT, computed tomography

morbidity ($P < 0.01$, Fisher's exact test). The mortality rate was highest in patients who had an anatomical resection (seven of 14 patients), and both of the patients who had repacking died from multiorgan failure. None of the six patients who had pack removal died, although two patients suffered morbidity.

Discussion

These data represent a selected group of patients. They do not include patients who were operated on at the primary hospital and were subsequently not stable enough for referral, nor do they include patients managed at a DGH following consultation with the liver unit or those who were managed appropriately in a DGH.

This series involved only 52 patients over a 10-year period, compared with more than 400 patients seen in a similar period in Cape Town, South Africa[13]. Violent injury is less common in the UK: it accounted for the majority of liver injury in other series[14], but for only 12 per cent of injuries in the present series. In series reported from South Africa[13] and the USA[15], penetrating trauma from gunshot and knife wounds accounted for 66–88 per cent of all liver injuries. In the present series, road traffic accidents resulting in blunt trauma made up the largest group of injuries, as reported in other European series[16].

There was no relationship between the mechanism of injury and the grade of liver injury, and no relationship between haemodynamic stability and either injury mechanism or grade of liver injury, unlike data from South Africa where mortality and morbidity were directly correlated with the mechanism of injury, which was itself correlated with grade of injury[13].

Liver trauma does not usually occur in isolation, and 36 of the 52 patients reported here had associated injuries, a rate similar to that of other series[17], although the presence of coexisting injuries had no bearing on either grade of liver injury or haemodynamic stability in the present series. A high index of suspicion is required in assessing potential liver injuries in multitrauma victims, because liver injury may not always be apparent on secondary survey[4]. The ATLS protocol emphasizes the importance of the 'golden hour' and the avoidance of delay in providing definitive treatment[4]. In this series, the median time to operation was 3 or 4 h. If these delays were inevitable, the time could have been utilized in the DGH to obtain appropriate imaging, to facilitate discussion and to arrange transfer to a tertiary centre.

In the majority of cases, even after a period of resuscitation to achieve haemodynamic stability, diagnostic imaging should be undertaken. Ultrasonography is favoured by many because of its portability[18,19], but over the past 10 years CT has become widely available and is relatively quick, with a high sensitivity and specificity[9,20]. CT may provide information on hepatic, splenic and intestinal injuries[21]. Despite the advantages of CT imaging of suspected liver injury, it is believed that the CT suite does not provide an environment in which resuscitation can continue safely. However, the literature contains no documented evidence that this is the case. The only study of CT in haemodynamically unstable patients following abdominal trauma reported on 50 patients, of whom 36 per cent were haemodynamically unstable at presentation, with no adverse outcome related to the CT procedure[22]. Provided adequate supervision of the patient in the imaging facility occurs whilst resuscitation continues, this should not adversely affect patient outcome. The availability of good-quality images will facilitate the diagnosis and organ injury scoring, and aid discussion and transfer to a specialist centre[1]. The absence of coexisting abdominal injuries may

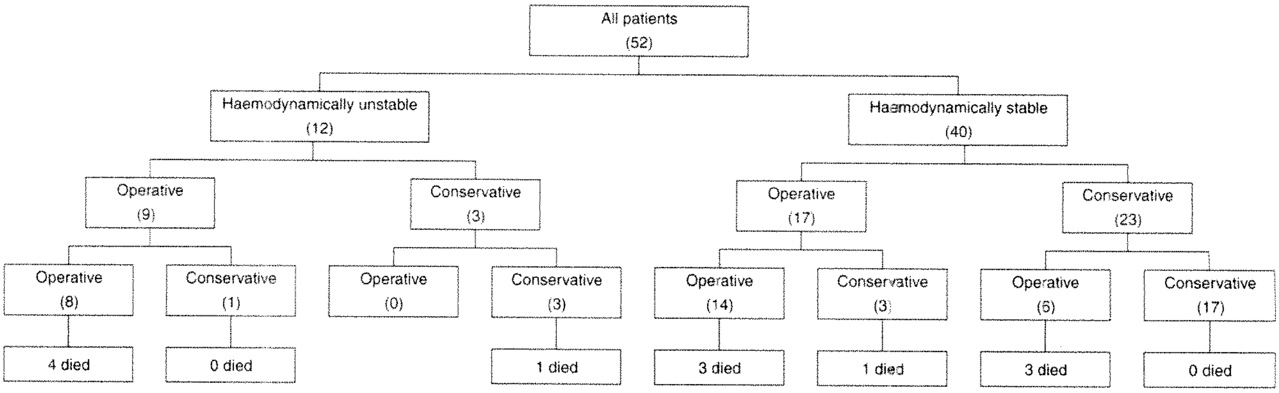

Fig. 2 Management and mortality in 52 patients treated in a district general hospital and subsequently referred to a specialist liver unit

provide the surgeon with the confidence to manage injuries conservatively as the primary management[23]. When haemodynamic stability cannot be achieved, however, the authors advocate immediate laparotomy without imaging, and discussion with a specialist centre once the extent of liver injury has been determined[24].

The adoption of a more conservative approach to abdominal injury, including liver and spleen injury, is becoming more widely utilized[11,16,25]. In this series, however, 26 (50 per cent) of the 52 patients were initially managed surgically, 16 of whom were haemodynamically stable. A conservative approach was used more commonly in patients who had an isolated liver injury. Twice the number of patients with other abdominal injuries and three times the number with long bone trauma were treated surgically. Of the 26 patients who were managed surgically at the referring hospital, 19 had liver injuries in isolation that were treated by packing with or without the addition of haemostatic sutures. Of the remaining patients, five had splenic injuries in addition to the liver injury and required emergency splenectomy.

Patients who had CT were less likely to be managed surgically. It is suggested that CT of liver injuries results in the adoption of a conservative approach to management, and this might result in correspondingly lower mortality and morbidity rates.

Liver injury is associated with high mortality and morbidity rates, and in this series the rates increased with severity of liver injury and the presence of coexisting injuries, similar to the findings of other reported series[17,26,27]. In the patients managed surgically at the primary hospital, mortality and morbidity rates were higher than in patients managed conservatively. The mortality rate in patients who required a second operation as part of the treatment was four times as high as that in patients who were managed conservatively throughout (*Fig. 2*). In the present series there was a high rate of anatomical resection, which carried with it the highest mortality rate. These facts are probably a reflection of the extent of parenchymal damage to the liver, and are similar to the findings of other series[1,28].

Following the introduction of changes to higher surgical training and the relative rarity of liver injury, it will become increasingly difficult for surgical trainees and future generations of consultants to gain sufficient surgical experience of the management of liver injury[29]. Effective management of liver trauma is not solely dependent upon surgical expertise. Conservative management of these injuries requires appropriate high-dependency care facilities and radiological expertise. These data suggest that early discussion with a specialist unit is essential and allows appropriate advice on conservative management, facilitates transfer to the specialist unit and, in the event of urgent surgical intervention being required, allows the availability of appropriate expertise.

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Short note

Long-term safety and efficacy of superficial femoral artery angioplasty with adjuvant photodynamic therapy to prevent restenosis

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Paper accepted 2 July 2002

Introduction

Percutaneous transluminal angioplasty is well established in the treatment of occlusive and stenotic atheromatous disease of arteries, but is limited by the development of restenosis[1]. Stenting markedly reduces early complications after coronary angioplasty, and shows a modest reduction in restenosis rates, but is less effective for femoropopliteal disease or in reducing restenosis rates. Restenosis can be reduced by coating stents with a cytostatic drug[2] or by brachytherapy, but another promising option is photodynamic therapy (PDT).

PDT involves the activation of a systemically administered photosensitizing agent by the application of non-thermal, non-ionizing radiation, usually by low-power red light from a laser[3]. This generates singlet oxygen, which in arteries ablates endothelial and medial smooth muscle cells by apoptosis without inducing inflammation[4]. In animal models of balloon injury to normal arteries, PDT inhibits intimal hyperplasia and reduces negative remodelling with no evidence of thrombosis, nor any impairment of the mechanical integrity of the arterial wall[3].

In 1999 the authors reported a pilot clinical study of adjuvant PDT in patients undergoing repeat superficial femoral angioplasty for restenosis[5]. Six months after PDT all patients were asymptomatic, there were no arterial complications and there was no evidence of restenosis. The present study documents the long-term outcome in these patients.

Patients and methods

All patients gave informed consent to the study, which was approved by the Joint University College London/University College London Hospitals Committee on the Ethics of Human Research. The original study included seven patients (aged 59–86 years) with symptomatic restenosis of the superficial femoral artery within 6 months of angioplasty (one with two lesions in the same artery). Each received 60 mg/kg of the photosensitizing agent 5-aminolaevulinic acid (ALA). Angioplasty was undertaken 4–6 h later, followed immediately by light delivery. The balloon guidewire was replaced by an optical fibre with a 4-cm diffuser tip, and red light (635 nm wavelength) was delivered to the dilated site via the optical fibre. The light source was a 635-nm diode laser.

The long-term safety and efficacy were assessed by clinical review and serial measurement of the peak systolic velocity ratio (PSVR) at the lesion site.

Results

The seven patients were followed for 42–51 (mean 48) months after PDT. None developed critical limb ischaemia or ulceration and there were no arterial complications. Only one patient had symptoms from restenosis at the site treated with adjuvant PDT (at which he had had two previous occlusions). He developed mild, non-limiting claudication 18 months after PDT, which has been stable for the past 2 years. His PSVR 29 months after PDT was 3·7 (the only measurement during follow-up that exceeded 2·0, the definition of restenosis). The other six patients were asymptomatic at the most recent review although one had experienced recurrent claudication 1 year after PDT and underwent repeat angioplasty to two new lesions. There was no evidence of restenosis at either of the PDT-treated sites in the same artery. Serial PSVR measurements at the PDT-treated sites for all patients are shown in *Fig. 1*.

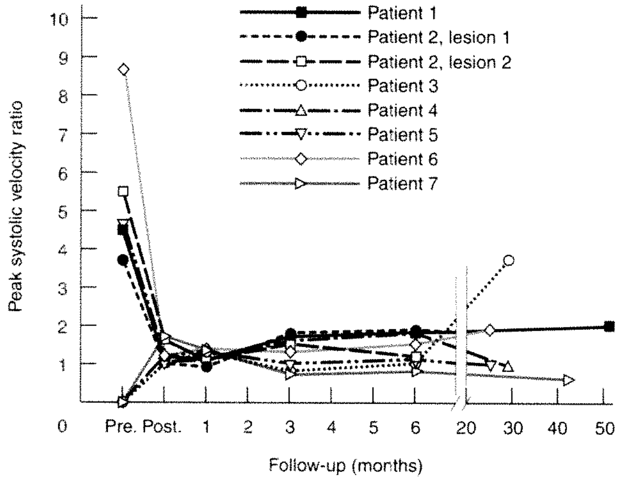

Fig. 1 Duplex follow-up imaging of the arterial segment that underwent angioplasty with adjuvant photodynamic therapy. Increasing peak systolic velocity ratio indicates increasing recurrent stenosis

Discussion

Only one of eight lesions treated by angioplasty with adjuvant PDT developed symptomatic restenosis at the treated site over a 4-year interval. Karch *et al.*[1] defined clinical success in claudicants as an improvement in walking distance greater than 50 per cent. With this definition, the only failure was due to disease progression other than at the site of PDT, giving a clinical success rate at 4 years of six of seven compared with 34 of 85 (40 per cent) in the series reported by Karch *et al.*[1].

PDT has several major attractions. It prolongs the angioplasty only by a few minutes and the risk of long-term complications seems low. It is well tolerated and requires only limited modification of existing angioplasty hardware. Extensive safety precautions, such as those for handling the radioactive materials used in brachytherapy, are not needed. When PDT-treated areas have healed, the artery resumes what is essentially a normal structure and the same area can be treated with PDT again if required. This is not true for brachytherapy, as all therapies based on ionizing radiation damage DNA, and there is a dose-related risk of permanent changes that may lead to long-term complications. Likewise with coated stents, animal studies have shown that the media remains thin and may remodel away from the stent struts[2].

This study was uncontrolled and the numbers are small. Nevertheless, adjunctive PDT does seem to hold considerable promise as a new strategy to prevent restenosis after angioplasty.

Acknowledgements

R.J.R.M. is supported by the British Heart Foundation. The original pilot study was funded by the Sir Jules Thorn Charitable Trust. ALA was supplied by DUSA Pharmaceuticals Inc. (Tarrytown, New York, USA). The authors thank Eileen Firman, research nurse, who assisted in the patient follow-up.

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Rectal washout with cytotoxic solution can be extended to the whole colon

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Background: Rectal irrigation with a cytotoxic agent does not kill viable intraluminal cancer cells proximal to the primary tumour. To prevent implantation of these cells at the time of restorative proctectomy, the feasibility of retrograde whole-colon irrigation just before surgery was explored.

Methods: The cytotoxic efficacy of different combinations of povidone–iodine (PVPI) and Gastrografin was tested with the trypan blue exclusion test on a human colon carcinoma cell line (SW620) *in vitro*. Subsequently, a retrograde whole-colon lavage with PVPI 5 per cent and Gastrografin 12 per cent was performed in 14 euthyroid, non-allergic patients with colorectal cancer using a colostomy irrigation set. Thyroid function and mucosal damage were assessed.

Results: It took 2 min and approximately 1 litre of infused solution to reach the caecum in all patients. The solution was 100 per cent tumoricidal *in vitro* and remained so after colonic irrigation. Total serum tri-iodothyronine (T3) levels decreased and those of reverse T3 increased, but normalized after 1 week. Superficial epithelial desquamation was observed shortly after irrigation; however, complete restoration occurred within 7 days.

Conclusion: A rectal washout can easily be extended to a retrograde irrigation of the whole colon in elective colorectal cancer surgery. This may help to prevent anastomotic and local recurrence due to implantation of viable exfoliated tumour cells.

Paper accepted 20 June 2002

British Journal of Surgery 2002, **89**, 1540–1544

Introduction

In patients with rectal cancer the rectum may be washed out with a cytotoxic agent, mainly povidone–iodine (PVPI), at the start of the procedure[1–4]. The rationale is to avoid suture-line recurrence due to implantation of viable exfoliated intraluminal cancer cells[5,6], and to prevent soiling and seeding of such cells during intraoperative division of the rectum[3,6]. Multiple clusters of malignant cells can be demonstrated on circular stapling devices after completion of an anastomosis during anterior resection for rectal cancer[7]. Furthermore, viable free cancer cells proximal to a large bowel carcinoma have been observed in 57 per cent of patients[8–14]. Recently, cancer recurrence at the longitudinal suture line of a colonic pouch has been documented in six patients after colon pouch–anal anastomosis despite rectal irrigation with a 5 per cent PVPI solution[15]. Antegrade colonic lavage with a cytotoxic agent has been used to kill exfoliated intraluminal cells[16,17]. While feasible, intraoperative on-table colonic irrigation might be considered tedious and time-consuming.

The present study was designed to evaluate the possibility of performing a retrograde colorectal washout in patients with non-stenosing rectal or colon cancer just before surgical resection. A secondary aim was to investigate the local and general side-effects of the cytotoxic agent as well as its *in vitro* tumoricidal efficacy on a human colon carcinoma cell line.

Patients and methods

In vitro tests

The cytotoxic effect of Gastrografin (N.V. Schering, Diegem, Belgium) at different concentrations (1, 3, 6 and 12 per cent), PVPI 5 per cent, Gastrografin 12 per cent mixed with PVPI 5 per cent in water, and PVPI 5 per cent in buffer (Braunol®; B. Braun Medical, Emmenbrücke, Switzerland) was tested on a human colon carcinoma cell line, SW620. Medium and water were used as controls. Cells were grown in monolayer culture in 75-cm^2 flasks using minimum essential medium (MEM) (Invitrogen, Merelbeke, Belgium) supplemented with antibiotics (penicillin 200 units/ml, vancomycin 100 µg/ml, gentamicin 50 µg/ml, amphotericin B 2·5 µg/ml), fetal calf serum 10 per cent, L-glutamine 2 mmol/l, insulin 20 munits/ml and dexamethasone 50 mmol/l. The cells were removed from the culture flasks by trypsinization. After removal of medium and washing of the cells with 10 ml sterile phosphate-buffered saline (PBS), 10 ml of a 1 : 10 solution of trypsin–ethylenediamine tetra-acetic acid (EDTA) in PBS was added (0·5 g trypsin in 250 ml EDTA 0·5 mmol/l). After incubation for 5 min at 37°C in 5 per cent carbon dioxide, the enzymatic reaction was stopped by addition of 20 ml Williams' medium E (Invitrogen) at 4°C. The cells were centrifuged at 150*g*, 4°C for 5 min, and the resulting cell pellet was resuspended in 3 ml MEM. At this stage tumour cell viability and concentration were assessed with the trypan blue test. The cell concentration was adjusted to about 4×10^6 cells per ml medium.

A 1-ml sample of this tumour cell suspension (TCS) was mixed with 9 ml of test solution and incubated at 37°C for 2 min. Some 40 ml of Williams' medium E at room temperature was then added in order to minimize further cytotoxic effects of the test solution during centrifugation and to reduce the density. The latter was necessary to collect the cells as a pellet after incubation in Gastrografin-containing solutions. The cell suspension was centrifuged (150*g*, 4°C for 5 min) and the pellet was resuspended in 1 ml MEM.

Samples from this final TCS were used in a trypan blue exclusion test. This test was performed by adding 500 µl trypan blue 0·4 per cent and 300 µl Gey's balanced salt solution to 200 µl TCS (about 8×10^5 cells). The test assesses the integrity of the cell membrane; cells with an intact cell membrane remain white, while blue cells with a leaking cell membrane are considered dead. The percentage of viable cells was calculated after counting at least 100 cells by light microscopy in a haemocytometer counting chamber at 200 × magnification. Three counts were performed for each sample.

The cytotoxic activity of the solution of PVPI 5 per cent and Gastrografin 12 per cent was tested before use in patients and in corresponding samples collected via the anus after colonic irrigation before the surgical procedure. Samples were centrifuged at 750*g*, 4°C for 15 min. Aliquots (9 ml) of the supernatant were used as test solution. For each patient, three tests were performed per test solution and per incubation time (0 and 2 min).

Patients

Fourteen patients, eight women and six men, underwent restorative proctectomy with colon pouch–anal anastomosis (eight patients), restorative proctectomy with ileocaecal interposition (one patient), sigmoid colectomy (two patients) or right hemicolectomy (three patients) for colorectal adenocarcinoma. Eight patients had preoperative radiochemotherapy (45 Gy + 5-fluorouracil). Age ranged from 41 to 80 (median 63) years, body-weight from 51 to 105 (median 71) kg and height from 147 to 180 (median 167) cm. The patients were all euthyroid. Renal function was normal and there was no iodine hypersensitivity. All patients had preoperative bowel preparation with Fleet Phospho-Soda® (Fleet, Lynchburg, Virginia, USA).

The study was approved by the local ethics committee and each patient gave informed consent to the procedure, including the application of techniques to prevent tumour recurrence and control examinations.

Whole-colon irrigation

After placement of an epidural catheter for postoperative patient-controlled analgesia and induction of general anaesthesia, the patient was placed in Lloyd-Davis leg holders. During placement of a central venous catheter, transanal irrigation with a mixture of Gastrografin 12 per cent and PVPI 5 per cent in water was performed using a colostomy irrigation set (Coloplast, Ruisbroek, Belgium). The irrigation reservoir was placed 1 m above the patient. The progress of the head of the retrograde colon irrigation was monitored with intermittent radioscopy. In the first six patients the time and quantity of enema needed to reach the splenic flexure, the hepatic flexure and the caecum were recorded. The radiation dose at the image intensifier was 11 µGy/s and the total fluoroscopy time was typically about 20 s. The effective dose was estimated by means of a commercially available software package (RADOS, Turku, Finland) and a series of measurements on the system. The effective dose for a man with a weight of 89 kg and a height of 1·73 m was 5·9 mSv. A woman of the same size would receive 6·2 mSv. The organ dose of the colon was 3·6 mSv, for both sexes. In the last eight patients radioscopy was only performed over the caecal region after infusion of 1 litre to confirm that the enema had reached the caecum. At the end of the irrigation, a rectal cannula was inserted to empty the colon. In five patients samples of the infused solution were collected from the anus for testing of their *in vitro* cytotoxic activity. At pouch construction the rest of the colon was eventually emptied further using a sump drain.

Systemic side-effects

Body temperature, and the cardiovascular, gastrointestinal and nervous systems were closely followed for symptoms of thyroid storm in all patients. Thyroid function was assessed in five patients, one woman and four men. Thyroid-stimulating hormone (TSH), total thyroxine (total T4), free T4, total tri-iodothyronine (total T3), reverse tri-iodothyronine (rT3), thyroxine-binding globulin (TBG) and resin T3 uptake (T3 RU) were measured in venous blood samples taken just before surgery, and 1, 3 and 7 days later.

Local side-effects

To assess mucosal alterations resulting from colonic lavage with Gastrografin 12 per cent and PVPI 5 per cent, biopsies of the rectum or neorectum were taken using a biopsy forceps in five patients. Biopsies were taken before irrigation, at the end of the surgical procedure and after 7 days.

Haematoxylin and eosin-stained sections from routinely formalin-fixed, paraffin-embedded material were assessed by light microscopy. The biopsies were assessed for features of mucosal damage including desquamation of the surface epithelium, less well differentiated light microscopic appearance of the epithelial cells, presence of oedema, congestion, haemorrhage and inflammatory cells in the lamina propria.

Statistical analysis

Values are given as mean(s.d.) or median (range) as indicated. Non-parametric tests were used to determine the statistical significance of thyroid hormone alterations before and after PVPI irrigation. Wilcoxon signed rank test was used for paired samples and Mann–Whitney *U* test for unpaired samples, or when considered appropriate. $P < 0.05$ (two-tailed) was considered significant.

Results

The mean(s.d.) viability of SW620 tumour cells after incubation for 2 min in Gastrografin 1, 3, 6 and 12 per cent was 89·6(0·1), 92·2(1·6), 93·1(2·3) and 90·0(4·0) per cent respectively, and did not differ significantly from control observations using MEM. A longer incubation of 15 min did not significantly affect tumour cell viability. No surviving cells were found after incubation with any of the solutions containing PVPI 5 per cent (*Table 1*). The cytotoxic effect of these solutions (PVPI 5 per cent and the combination with Gastrografin 12 per cent) was not influenced by the time from preparation to use or by temperature. Whether the PVPI 5 per cent solutions were prepared *ex tempore* or 30 min, 1, 3, 4, 6 or 24 h before the experiment, cell viability as assessed by the trypan blue test was always zero. Identical results were observed when using the solutions at room temperature or at 4°C.

Physical characteristics, including pH and osmolality of the different test solutions, were determined (*Table 1*). PVPI 5 per cent and PVPI 5 per cent + Gastrografin 12 per cent had an acid pH of 2·1 and 2·8 respectively. Therefore, a commercially available solution of PVPI in buffer (Braunol® 5 per cent, pH 6·1) was tested for its cytotoxic effect *in vitro*. Incubation of SW620 cells with Braunol® also resulted in 100 per cent death of the cells after 2 min. PVPI and Braunol® were equally effective in hypotonic (water) and hypertonic (Gastrografin) solution.

Retrograde irrigation of the whole colon was achieved in all 14 patients. A median of 940 ml of solution (range 700–1200 ml) was employed. The enema reached the splenic flexure, hepatic flexure and caecum in a median of 53, 90 and 120 (range 85–150) s respectively. Thus the whole procedure was completed within 5 min.

All patients recovered well from the operation without symptoms of acute iodism. The serum levels of T3 RU and TSH were decreased 1 day after surgery, but started to recover on day 3. Serum total T3 levels decreased significantly 1 day after surgery but normalized on day 7. Serum TBG and total and free T4 levels were not influenced, while serum rT3 levels increased significantly after colonic irrigation. One week after operation, almost all markers of thyroid function had normalized (*Table 2*).

A mucous anal discharge was noticed after the operation, which ceased within 2–3 days. No anastomotic leaks were observed. The median postoperative hospital stay was 11 (range 6–24) days. Histological assessment before irrigation revealed only mild oedema of the rectal mucosa in four of five patients. After irrigation, desquamation of the surface epithelium was recorded in three patients, accompanied by mild intramucosal haemorrhage in two. In the remaining two patients the mucosa appeared unaltered. At follow-up (7 days) the epithelial lining was intact in all patients, while the lamina propria was still mildly oedematous in two. An inflammatory infiltrate was not found at any time.

Discussion

Local recurrence after potentially curative colorectal cancer surgery has been reported to develop at the suture line in between 6 and 37 per cent of patients[5,6,18]. Implantation of intraluminal viable exfoliated malignant cells may be responsible[18–20]. This hypothesis prompted the use of operative measures to kill these cells or to limit implanta-

Table 1 Physical characteristics and *in vitro* cytocidal activity of test solutions

Solution	pH	Osmolality (mmol/kg)	No. of tests	Tumour cell viability (trypan blue test) 2-min incubation	Tumour cell viability (trypan blue test) Without incubation
MEM	8·4	296(0)	14	96(2)	94(4)
Water	6·8	13(3)	15	55(16)	77(7)
Gastrografin 12%	7·5	557(3)	6	90(4)	–
PVPI 5%	2·1	61(1)	10	0	0
PVPI 5% + Gastrografin 12%	2·8	617(1)	10	0	0
Braunol® 5%	6·1	91(3)	10	0	0
Braunol® 5% + Gastrografin 12%	4·8	872(1)	10	0	0
Sample from *in vivo*	–	–	15	0	0

Values are mean(s.d.). MEM, minimum essential medium; PVPI, povidone–iodine

Table 2 Effect of retrograde whole-colon irrigation with povidine–iodine 5 per cent on thyroid function

Assay	Baseline	Day 1	Day 3	Day 7	Laboratory reference range
TSH (munits/l)	1·15 (0·32–2·49)	0·5 (0·27–3·54)	0·38 (0·29–4·40)	1·87 (0·60–3·55)	0·15–4·60
Total T4 (μg/dl)	7·5 (6·4–9·4)	7·3 (5·9–8·5)	7·3 (6·1–8·4)	10·3 (8·1–10·9)	5·5–12·0
Free T4 (ng/dl)	1·6 (1·3–1·7)	1·6 (1·3–2·2)	1·6 (1·2–2·3)	1·9 (1·7–2·0)	0·7–1·9
Total T3 (ng/dl)	75 (69–124)	48 (38–55)	60 (45–69)	93 (54–122)	80–190
rT3 (mg/dl)	42 (20–43)	58 (52–85)	79 (36–97)	75 (44–108)	20–50
T3 RU (%)	88 (79–101)	78 (77–85)	88 (70–100)	95 (75–104)	90–118
TBG (mg/dl)	18 (16–24)	18 (15–21)	19 (17–23)	21 (17–24)	14–24

Values are median (range); *n* = 5. TSH, thyroid-stimulating hormone; T4, thyroxine; T3, tri-iodothyronine; rT3, reverse T3; T3 RU, resin T3 uptake; TBG, thyroxine-binding globulin

tion. The intraluminal application of one of several tumoricidal agents has been advocated[5,9,21] and reported to reduce the incidence of suture-line recurrence from 10–16 per cent to 2–3 per cent[5,10,21]. PVPI solution is the most frequently used agent: it is cheap, easy to use, bactericidal and devoid of clinically relevant local or systemic side-effects[4,16,22–27]. A 5 per cent solution is recommended because PVPI 1 per cent may be inactivated *in vivo* by organic substances[28].

Most surgeons only perform rectal irrigation in patients with rectal cancer, both at the beginning of the procedure and after placement of a clamp below the tumour before stapling[4]. The tumour-bearing bowel segment and the colon proximal to the tumour, however, are not irrigated except in cases of low rectal cancer. In this way tumour breach or accidental laceration of the bowel wall occurring during rectal resection may result in the spillage of cancer cells. Furthermore, untreated exfoliated cancer cells in the descending colon[12] may be entrapped in the stapled anastomosis during coloanal anastomosis and pouch construction[7,15]. To prevent suture-line recurrence as well as rectal tumour cell soiling due to perforation, an intraoperative whole-colon washout with PVPI has been proposed. In an experimental study in rats, the risk of anastomotic recurrence was significantly reduced[17]. In a clinical study, on-table whole-colon washout was found to be safe and feasible, but it prolonged operating time by 20–30 min[16]. The current study was undertaken to test a simplification of the method.

A whole-colon washout with 1 litre PVPI 5 per cent solution can be performed easily in less than 5 min by retrograde irrigation using a colostomy irrigation set. A contrast medium, Gastrografin 12 per cent, was used for visualization of the head of the enema under radioscopy. The *in vitro* study showed that Gastrografin itself has no cytotoxic effect on cells. As already observed, 5 per cent PVPI kills 100 per cent of tumour cells. The admixture of Gastrografin with PVPI did not affect the *in vitro* cytotoxic efficacy of the latter. The solution collected via the anus after irrigation did not contain any viable cells and maintained its cytotoxicity. The PVPI solution can be prepared in advance. Complementary studies strongly suggest that the cytotoxic effect of PVPI solutions is mainly due to the iodine component and not to the pH or osmolality of the solution.

Repeat testing of local and general effects confirmed earlier observations that side-effects of a PVPI 5 per cent colon irrigation are minor and temporary, with all variables tested normalizing within 7 days in almost all patients[16]. The temporary effects on thyroid function can be explained either by the acutely increased availability of iodine after whole-colon irrigation (increased rT3) or by the stress response after surgical trauma.

A limited rectal washout with PVPI 5 per cent can easily and safely be extended to a whole-colon washout by retrograde irrigation using a colostomy irrigation set in elective colorectal cancer surgery. By killing free intraluminal viable cancer cells this procedure may prevent tumour cell implantation on anastomotic lines as well as accidental peritoneal cell soiling due to iatrogenic perforation of the tumour-bearing bowel segment.

Acknowledgements

The authors are grateful to J. Billen, Clinical Laboratory, University Clinic Gasthuisberg, Leuven, for the thyroid tests, M. Dooms, pharmacist, for preparation of the antiseptic solutions, and Mrs H. Bosmans, engineer in radiophysics, for radiation dosimetry.

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Original article

Peritoneal carcinomatosis from colorectal cancer

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Background: Aggressive therapeutic regimens have been advocated for the treatment of peritoneal carcinomatosis from colorectal cancer. It is essential to understand the clinical and histological features that govern the natural history of this condition if the efficacies of novel therapeutic approaches are to be assessed adequately.

Methods: A database of 3019 colorectal cancers was used to identify patients with synchronous peritoneal carcinomatosis, patients who developed metachronous peritoneal carcinomatosis, and those without carcinomatosis. Clinical, histological and survival data for the groups were collated and subjected to statistical analysis.

Results: Some 349 patients (13 per cent) with peritoneal carcinomatosis were identified; 214 had synchronous disease and 135 had metachronous carcinomatosis. Some 125 patients (58 per cent) in the synchronous group were free of systemic metastases; 80 of these patients had localized disease. Liver metastases, tumour (T) stage, nodal stage, and venous and perineural invasion were independent predictors of metachronous carcinomatosis. The median survival of patients with synchronous disease was 7 months; survival was adversely affected by the extent of peritoneal carcinomatosis and the T stage of the primary cancer.

Conclusion: Peritoneal carcinomatosis is a common mode of disease progression in patients with colorectal cancer. For the majority of patients the prognosis is poor, but a small number with localized disease may be suitable for further aggressive therapy.

Paper accepted 23 July 2002

British Journal of Surgery 2002, 89, 1545–1550

Introduction

Peritoneal carcinomatosis is not an uncommon mode of disease progression from colorectal cancer, yet relatively little has been documented regarding its clinical and histological features. An appreciation of these aspects is fundamental to an understanding of the natural history of the disease and to the interpretation of the efficacy of new treatment modalities.

Because of its poor prognosis (median survival 5–6 months[1,2]), colorectal peritoneal carcinomatosis has previously been considered a preterminal condition suitable only for palliative treatment. The introduction of cytoreductive surgical techniques[3] combined with intraperitoneal chemotherapy regimens promises to improve long-term survival for selected patients with peritoneal carcinomatosis[4]. While the initial results utilizing these techniques have been promising, caution must be exercised before recommending them as first-line treatment modalities. The morbidity and mortality associated with combined cytoreduction and intraperitoneal chemotherapy are high[5–8], and survival data from randomized controlled trials are not available. Only patients with low-volume, low-grade peritoneal disease, with no evidence of systemic spread, appear to benefit from this radical approach[9,10]. Moreover, optimal results are achieved only if complete cytoreduction is performed with no tumour deposits greater than 2·5 mm left behind at operation[9,11].

The aims of the study were fourfold: (1) utilizing a large prospective database, to determine the incidence of peritoneal carcinomatosis from colorectal cancer; (2) to describe the clinical and histological features in patients with synchronous peritoneal carcinomatosis present at the time of diagnosis of the primary colorectal cancer, in those presenting with metachronous peritoneal carcinomatosis after 'curative' colorectal surgery, and in patients who never develop carcinomatosis; (3) to analyse the clinical and histological predictors for the development of metachronous disease, and the predictors of survival for patients with synchronous carcinomatosis; and (4) to estimate the number of patients who might benefit from aggressive interventions such as cytoreductive surgery and intraperitoneal chemotherapy.

Patients and methods

Preoperative, operative and follow-up data on all patients presenting with colorectal cancer to Singapore General Hospital between April 1989 and March 1999 were retrieved from a departmental computer database. All data had been entered prospectively and updated on a regular basis. The data were sorted and entered into a statistical software package (Statistical Package for the Social Sciences version 10; SPSS®, Chicago, Illinois, USA). Missing data were retrieved from patient case notes where possible, and any ambiguous entries corroborated by reference to their original source (e.g. operating notes, histology reports).

For analysis, patients were classified into three groups: those with synchronous peritoneal carcinomatosis; those who developed metachronous disease; and those who never developed carcinomatosis.

Patients with synchronous disease were diagnosed at the time of presentation with colorectal cancer, either on routine staging, computed tomography (CT) or at laparotomy. Patients with metachronous carcinomatosis were deemed to be clear of peritoneal disease at the initial 'curative' colorectal resection, but subsequently became symptomatic on follow-up and were diagnosed with peritoneal metastases on CT. The extent of peritoneal involvement was defined as localized if only one of the five abdominal and pelvic regions was deemed to be involved at laparotomy or CT, and as generalized if two or more regions were involved. The 'no carcinomatosis' group consisted of patients without peritoneal disease at initial colorectal resection and no evidence of peritoneal carcinomatosis on clinical or radiological follow-up.

Postoperative follow-up was dictated by departmental policy, and consisted of 3-monthly outpatient assessment for 3 years, followed by 6-monthly appointments. Carcinoembryonic antigen levels were determined before operation and at each outpatient visit. Surveillance colonoscopy and CT were performed routinely 1 year after operation and repeated as appropriate for the individual thereafter.

Demographic details of the three groups were compiled, along with clinical variables recorded at the time of initial operation (tumour site, tumour size, complicating features of obstruction or perforation, the presence of liver metastases and ascites) and histological details of the resected specimen (tumour (T) stage, nodal (N) stage, tumour differentiation, and evidence of microscopic venous and perineural invasion). These data were collated with survival data obtained from prospective follow-up.

Clinical and histological parameters of the three groups were compared with the Mann–Whitney *U* or Kruskal–Wallis test for continuous data and with the χ^2 test for categorical variables. $P < 0{\cdot}05$ was considered statistically significant. Predictive indicators for the development of metachronous peritoneal carcinomatosis were identified by comparing the metachronous and 'no carcinomatosis' groups using logistic regression modelling. Survival data for patients with synchronous carcinomatosis were analysed by means of the Kaplan–Meier method with log rank significance testing. Variables found to be significant were subjected to Cox regression modelling to determine predictors of survival.

Results

A total of 3019 patients with a diagnosis of colorectal cancer was identified from the database. Of these, complete clinical and histological data were available in 2756 (91 per cent) of patients, and this cohort was used for subsequent analysis. Some 349 patients (13 per cent) were identified with peritoneal carcinomatosis, 214 (61 per cent) of whom formed the synchronous carcinomatosis group, 135 (39 per cent) the metachronous disease group, and the remaining 2407 patients comprised the 'no carcinomatosis' group.

There was no difference between the three groups in terms of gender or age at presentation. The median age at presentation was 62 (interquartile range (i.q.r.) 51–72) years for patients with synchronous carcinomatosis, 65 (i.q.r. 52–72) years for those with metachronous disease, and 64 (i.q.r. 54–73) years for those with no carcinomatosis.

Of the 214 patients with synchronous peritoneal carcinomatosis, 125 (58 per cent) had peritoneal metastases as the only form of tumour dissemination with no clinical or radiological evidence of other systemic spread. The majority of these (80 (64 per cent) of 125) were considered to have localized carcinomatosis, and 41 (33 per cent) had generalized disease. The extent of dissemination was unclear in four patients. It was not possible to determine the extent of disease accurately in the metachronous disease group, as not all patients were subjected to laparotomy.

Clinical features

The clinical features of the three groups are given in *Table 1*. Univariate analysis showed no difference between the three groups in terms of tumour site, tumour size, or complicating features of obstruction or perforation. The presence of liver metastases and ascites were both significantly greater in the synchronous and metachronous carcinomatosis

Table 1 Comparison of the demographic and clinical characteristics of patients with synchronous, metachronous and no peritoneal carcinomatosis at initial presentation with colorectal cancer

	Peritoneal carcinomatosis			
	Synchronous (*n* = 214)	Metachronous (*n* = 135)	None (*n* = 2407)	*P*
Sex ratio (M : F)	1 : 1·1	1 : 1·2	1·2 : 1	n.s.*
Median (i.q.r.) age (years)	62 (51–72)	65 (52–72)	64 (54–73)	n.s.†
Site				n.s.*
Right	34 (16)	18 (13)	303 (13)	
Transverse	14 (7)	8 (6)	127 (5)	
Left	53 (25)	36 (27)	696 (29)	
Rectum	113 (53)	73 (54)	1281 (53)	
Median (i.q.r.) size (cm)	5 (3–6)	4 (3–6)	5 (4–6)	n.s.†
Liver metastases				< 0·001*
Present	89 (42)	45 (33)	251 (10)	
Absent	125 (58)	90 (67)	2156 (90)	
Ascites				< 0·001*
Present	60 (28)	28 (21)	270 (11)	
Absent	154 (72)	107 (79)	2137 (89)	
Complications				n.s.*
None	176 (82)	115 (85)	1885 (78)	
Obstruction	17 (8)	13 (10)	385 (16)	
Perforation	21 (10)	7 (5)	137 (6)	

Values in parentheses are percentages unless indicated otherwise. i.q.r., Interquartile range; n.s., not significant. $^*\chi^2$ test; †Kruskal–Wallis test

Table 2 Logistic regression analysis for the development of metachronous peritoneal carcinomatosis following 'curative' operation

	Odds ratio	*P*
Clinical		
Liver metastases	2·84 (1·73, 4·67)	< 0·001
Histological		
Tumour stage	2·74 (1·66, 4·52)	< 0·001
Nodal stage	2·47 (1·60, 3·82)	< 0·001
Venous invasion	2·07 (1·17, 2·39)	0·012
Perineural invasion	1·57 (1·03, 2·39)	0·032

Values in parentheses are 95 per cent confidence intervals

groups than in patients without carcinomatosis (P < 0·001). Logistic regression analysis, comparing patients with metachronous disease with those without carcinomatosis (*Table 2*), led to the exclusion of all clinical variables except the presence of liver metastases as independent predictors for the development of peritoneal carcinomatosis (odds ratio (OR) 2·84 (95 per cent confidence interval (c.i.) 1·73 to 4·67); P < 0·001).

Treatment of patients with synchronous peritoneal carcinomatosis consisted of surgical resection of the colorectal primary combined with debulking of the peritoneal metastases, where appropriate, in 155 (72 per cent) of 214 patients. In 42 patients (20 per cent) resection of the primary tumour was not performed: 13 patients undergoing gastrointestinal bypass, 20 having a defunctioning colostomy, and nine only a biopsy. The remaining 17 patients (8 per cent) were not subjected to any surgical intervention.

Of the 135 patients with metachronous carcinomatosis, only ten (7 per cent) underwent surgical intervention. Three of these had metastases confined to the peritoneal cavity, of whom two underwent anterior resection as treatment for pelvic peritoneal recurrence and one had a palliative colonic resection. Of the remaining seven patients with coexistent systemic metastases and peritoneal carcinomatosis, one underwent an anterior resection and urinary bypass, four had a colonic bypass, and two a Hartmann procedure.

Histological features

The histological features of the primary tumours are shown in *Table 3*. On univariate analysis, all of the parameters analysed (T stage, N stage, differentiation, venous invasion, perineural invasion) showed a significant difference between the three groups, with patients in the synchronous and metachronous carcinomatosis groups having a higher proportion of tumours with features of advanced stage. Logistic regression analysis, comparing the metachronous and 'no carcinomatosis' groups, led to the exclusion of tumour differentiation as an independent predictor of peritoneal carcinomatosis. ORs for developing metachro-

Table 3 Comparison of histological findings for primary tumours in patients with synchronous, metachronous and no peritoneal carcinomatosis

	Peritoneal carcinomatosis			
	Synchronous (n = 214)	Metachronous (n = 135)	None (n = 2407)	P^*
Tumour stage				< 0·001
T1	0 (0)	4 (3)	96 (4)	
T2	2 (1)	2 (1)	265 (11)	
T3	127 (59)	104 (77)	1878 (78)	
T4	85 (40)	25 (19)	168 (7)	
Nodal stage				< 0·001
N0	83 (39)	43 (32)	1334 (55)	
N1	37 (17)	28 (21)	707 (29)	
N2	94 (44)	64 (47)	366 (15)	
Differentiation				< 0·001
Well	8 (4)	5 (4)	125 (5)	
Moderate	150 (70)	100 (74)	1982 (82)	
Poor	56 (26)	30 (22)	300 (12)	
Venous invasion				< 0·001
Present	27 (13)	18 (13)	93 (4)	
Absent	187 (87)	117 (87)	2314 (96)	
Perineural invasion				< 0·001
Present	55 (26)	47 (35)	221 (9)	
Absent	159 (74)	88 (65)	2186 (91)	

Values in parentheses are percentages. $^*\chi^2$ test

nous disease after 'curative' operation were derived from the logistic regression model, and are given for each variable in *Table 2*.

Survival data

Crude survival data were available for 253 patients with peritoneal carcinomatosis: 161 (75 per cent) of patients in the synchronous carcinomatosis group and 92 (68 per cent) of those in the metachronous disease group. Survival data for the remaining patients were incomplete as a result of the status of Singapore General Hospital as a tertiary referral centre for colorectal cancer for much of South-East Asia, which presents geographical problems for long-term follow-up. From the available data, median survival for the synchronous group was 7 (i.q.r. 2–11) months. Within this group, patients with localized peritoneal carcinomatosis survived significantly longer than those with generalized carcinomatosis: median 9 (i.q.r. 3–16) months for localized disease *versus* 4 (2–9) months for generalized peritoneal carcinomatosis (P = 0·004). The median survival for patients with metachronous carcinomatosis was 28 (i.q.r. 18–36) months from the initial diagnosis of colorectal cancer. As expected, this was significantly longer than that in patients with synchronous disease (P < 0·001), and reflected a median time to diagnosis of metachronous carcinomatosis of 16 (i.q.r. 10–25) months.

Survival analysis for patients with synchronous peritoneal carcinomatosis showed that the extent of disease (localized *versus* generalized peritoneal carcinomatosis) was the only significant clinical predictor of survival on both univariate and Cox regression analysis (OR 1·90 (95 per cent c.i. 1·17 to 3·14); P < 0·009). Univariate analysis of the histological parameters revealed that both T stage and grade of differentiation predicted length of survival. However, differentiation was excluded on multivariate regression, leaving T stage as the only histological predictor of survival (OR 1·68 (95 per cent c.i. 1·14 to 2·46); P = 0·008).

Discussion

Surprisingly little has been documented about the clinical and histological features of peritoneal carcinomatosis from colorectal cancer. In 1989, Chu *et al.*[1] analysed the prognostic indicators for 100 patients with peritoneal carcinomatosis of non-gynaecological origin, only 45 of whom had primary colorectal cancer. The large multicentre Evolution of Peritoneal Carcinomatosis (EVOCAPE 1) study[2] included only 118 patients with colorectal peritoneal carcinomatosis. The present analysis of 2756 patients with colorectal cancer including 349 with peritoneal carcinomatosis of large-bowel origin is the largest cohort reported to date.

In determining which patients develop metachronous carcinomatosis after 'curative' operation, the presence of liver metastasis, T stage, N stage, and venous and perineural invasion were all found to be independent predictors. Unfortunately, intraperitoneal chemotherapy is of limited benefit in patients with systemic metastases[12], making the presence of liver metastases redundant as an indicator for this kind of therapy. In addition, for maximal efficacy, intraperitoneal chemotherapy should be started as soon as possible after operation[13], before the availability of formal histological analysis. The use of currently available histological parameters as indicators for adjuvant intraperitoneal chemotherapy is therefore also restricted, and additional markers of peritoneal carcinomatosis, such as positive peritoneal cytology findings that can be determined quickly during the perioperative period, may prove to be of more value.

In their analysis of prognostic factors associated with peritoneal carcinomatosis, Chu *et al.*[1] found that on univariate analysis a disease-free interval of less than 1 year, the presence of ascites and lung metastasis had a significant adverse effect, whereas the presence of liver metastases and the extent of peritoneal carcinomatosis did not affect patient survival. In the present series several factors (extent of peritoneal carcinomatosis, primary tumour site, presence of liver metastases, ascites, T stage of the primary tumour, and differentiation) were associated with adverse survival on univariate testing. However, only the extent of carcinomatosis and primary T stage retained their significance on Cox regression modelling. These findings are more in keeping with those of the EVOCAPE 1 trial, in which the extent of carcinomatosis and T stage of the primary tumour were also the only significant predictors of survival. In patients being considered for operation, the extent of peritoneal carcinomatosis appears to be the only preoperative indicator of survival and should be taken into consideration, along with other more subjective factors such as performance status[14], when estimating the benefits of surgical intervention.

The introduction of aggressive cytoreductive procedures[3] combined with intraperitoneal chemotherapy promises to radically alter our thinking about the treatment of patients with colorectal peritoneal carcinomatosis. Of the available intraperitoneal chemotherapeutic regimens, intraperitoneal chemohyperthermia (IPCH) appears to be the most effective in terms of survival benefit, with several series reporting 2- and 5-year survival rates of 45–60 and 20–30 per cent respectively[15–17]. IPCH can be used either as a primary treatment for peritoneal carcinomatosis, in combination with cytoreductive surgery, or as a prophylactic therapy in those at high risk of developing metachronous peritoneal carcinomatosis. The current indications for prophylactic IPCH include perforated cancers, cancers adherent to adjacent structures, overt tumour spillage at operation, and positive peritoneal lavage[11]. The present finding of T stage as an independent predictor of metachronous peritoneal carcinomatosis supports the use of prophylactic IPCH in patients in whom tumour cells have direct access to the peritoneal cavity. Although tumour perforation is a well recognized risk factor for local recurrence[18–20], it was not possible to comment on its effect on the development of peritoneal carcinomatosis because the database did not allow discrimination of tumours that had perforated spontaneously from those that caused secondary colonic perforation. The presence of overt lymph node metastases might also be added to the list of indications for IPCH, as it increases the risk of subsequent metachronous disease by a factor of 2·5.

Overall, the incidence of colorectal peritoneal carcinomatosis was found to be 13 per cent, which is comparable to other reports[21]. A total of 80 patients with synchronous carcinomatosis had localized disease in the absence of systemic metastases. This represents 3 per cent (80 of 2756) of the study population that might have derived some benefit from cytoreductive surgery and IPCH. In Singapore, with an annual incidence of colorectal cancer of 2500 cases per annum[22], this equates to approximately 70 patients per year, or translated into UK practice, with an annual incidence of 34 000 colorectal cancers per annum[23], approximately 1000 patients who might benefit from these treatments.

Although the benefits of cytoreductive surgery and IPCH have yet to be validated in randomized trials, there is a growing enthusiasm for this treatment particularly in the West. This is understandable, given the promising results achieved to date, particularly when viewed against the dismal prognosis associated with previous treatments.

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Original article

Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer

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Background: Bladder and sexual dysfunction, secondary to pelvic nerve injury, are recognized complications of rectal resection. This study investigated the frequency of these complications following laparoscopically assisted and conventional open mesorectal resection for cancer.

Methods: A total of 170 patients with rectal cancer was identified from a previous randomized trial of laparoscopic *versus* open resection. A retrospective analysis of bladder and sexual function before and after operation was performed by means of postal questionnaires and telephone interviews.

Results: At the time of the study, 111 (65 per cent) of the 170 patients were alive, of whom 80 (72 per cent) responded. Of the responders, 40 patients had undergone laparoscopically assisted resection and 40 had had an open operation. No significant deterioration in bladder function following operation was observed, although two patients in the laparoscopic group required long-term intermittent self-catheterization. A significant difference in male, but not female, sexual function was noted, with seven of 15 sexually active men in the laparoscopic group reporting impotence or impaired ejaculation, compared with only one of 22 patients having an open operation ($P = 0.004$). All patients with bladder or sexual dysfunction in the laparoscopic group had resection of either bulky or low rectal cancers.

Conclusion: Laparoscopically assisted rectal resection is associated with a higher rate of male sexual dysfunction, but not bladder dysfunction, compared with the open approach. This has implications, particularly for sexually active males with bulky or low rectal cancers, when deciding the best operative approach.

Paper accepted 23 July 2002

British Journal of Surgery 2002, **89**, 1551–1556

Introduction

Bladder and sexual dysfunction are recognized complications following surgical resection of the rectum. The incidence varies greatly, with reported values of 8–54 per cent for bladder dysfunction[1–3] and 18–59 per cent for sexual dysfunction[4–11]. The incidence is dependent on the extent of resection[12] and the surgical technique employed.

Total mesorectal excision (TME) is the preferred method for oncological resection of low rectal cancers. It achieves complete excision of the rectum together with its draining lymphatics, and results in low rates of local recurrence[13,14]. For cancers of the mid and upper rectum, wide mesorectal excision (WME) is often preferred to TME, with preservation of the uninvolved lower rectum. Both techniques employ dissection in the tissue plane that separates the mesorectal fascial envelope from the presacral fascia[13]. However, care must be exercised because excessive traction during the dissection or lateral dissection outside this plane may lead to neuropraxia or permanent injury to the sympathetic and parasympathetic nerves that course along the lateral pelvic side-walls. Inadvertent damage to these nerves will result in postoperative bladder and sexual dysfunction, the severity of which will be dependent on the extent of the injury and the relative components of the autonomic supply affected[10,15,16].

Laparoscopic resection of the rectum has been shown to achieve oncological tumour clearance equivalent to that of conventional open operation, with the potential benefits of reduced pain, shorter hospital stay and earlier return to normal function[17–20]. The results of large randomized multicentre trials[21–23] are eagerly awaited to determine the cost-effectiveness of laparoscopic surgery in malignant disease[24] and its influence on local recurrence rates and long-term survival. Although technically more demanding and associated with a long learning curve[25], the magnified view of the pelvis afforded by the laparoscope[26] may facilitate identification of the autonomic nerves and thus prevent inadvertent injury. The rates of bladder and sexual dysfunction following laparoscopic rectal resection have not been reported previously. The authors therefore conducted a retrospective analysis of bladder and sexual function in patients who had undergone rectal resection as part of a previous randomized trial of laparoscopically assisted *versus* conventional open operation for colorectal malignancy[27].

Patients and methods

One hundred and seventy patients with a diagnosis of rectal cancer were identified from a database of 250 patients previously enrolled in a randomized trial of laparoscopically assisted *versus* open operation for colorectal cancer[27]. The medical records and histological reports of all patients were scrutinized for details of patient demographics, operative technique, postoperative complications and follow-up progress.

Within the confines of the trial, patients had been randomized to either laparoscopic or open operation by means of computer generation. All patients had been prepared for operation, as per the trial protocol, with oral osmotic bowel preparation, low molecular weight heparin and prophylactic antibiotics.

Patients randomized to open operation underwent resection according to standard oncological practice. This included sharp diathermy mobilization of the left colon, and if necessary of the splenic flexure, high ligation of the inferior mesenteric pedicle, *en bloc* resection of involved adjacent organs and sharp diathermy mobilization of the rectum within the mesorectal plane. TME or WME was dictated by the height of the tumour. Anastomoses were performed using established stapling techniques and defunctioned at the discretion of the surgeon. Patients with low tumours (less than 5 cm from the anal verge), in whom oncological resection was not possible without compromise of the sphincter complex, underwent abdominoperineal resection.

Patients randomized to the laparoscopic group underwent rectal resection according to the same oncological principles outlined for open surgery. Generally, a four-port technique was employed, supplemented by an additional fifth port as necessary, with pneumoperitoneum not exceeding a pressure of 12 mmHg. Sharp diathermy mobilization of the left colon, and if necessary of the splenic flexure, was followed by intracorporeal ligation of the inferior mesenteric pedicle using an endovascular stapler. Mobilization of the rectum in the mesorectal plane was performed to a level below the distal edge of the tumour. A small suprapubic incision was made, the dissection completed, and the rectum divided. Anastomoses were performed using similar stapling techniques to those used in the open procedure, and defunctioned at the discretion of the surgeon. For laparoscopically assisted abdominoperineal resections, the abdominal operation was carried out in a similar fashion but with intracorporeal division of the proximal colon, formation of an end-colostomy, and delivery of the specimen through the perineal wound.

Structured postal questionnaires based on previously validated instruments were utilized to assess patients' bladder and sexual function before and at least 1 year after operation. The international prostatic symptom score (I-PSS)[28], with minor modification, was used to assess bladder function, with additional questions to assess urinary incontinence and the need for intermittent self-catheterization. The international index of erectile function[29] was used to assess male sexual function, with emphasis on domains to evaluate erectile function, ejaculatory function, sexual desire and overall sexual satisfaction. Female sexual function was assessed by evaluation of sexual desire, dyspareunia and sexual satisfaction[30]. The postal survey was supplemented by follow-up telephone interviews to validate the information retrieved and clarify any areas of discrepancy.

Statistical analysis

Data on patient demographics, operative details, histological details, and preoperative and postoperative bladder and sexual function were entered into a statistical software package (Statistical Package for the Social Sciences version 9.0; SPSS®, Chicago, Illinois, USA), and analysed using the Mann–Whitney *U* test or Wilcoxon signed ranks test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Differences in preoperative and postoperative bladder and sexual dysfunction between the two groups were analysed on an intention-to-treat basis.

Results

Of the 170 patients analysed, 86 (51 per cent) were randomized to the laparoscopic group and 84 (49 per cent) to open operation. Patient demographics, operative details and histological data are shown in *Table 1*. There was no statistically significant difference between the groups in terms of age, sex distribution, the number and types of operative procedures performed, or the tumour (T) and nodal (N) stages of the resected specimens. In total, 47 per cent of patients underwent high anterior resection, 41 per cent had low anterior resection, and 9 per cent had

Table 1 Demographic and clinical characteristics of patients undergoing laparoscopically assisted or conventional open resection of rectal cancer

	Laparoscopic approach (*n* = 86)	Open operation (*n* = 84)
Median (i.q.r.) age (years)	64 (53–69)	62 (55–69)
Sex ratio (M : F)	42 : 44	52 : 32
Operation		
High anterior resection	42 (49)	38 (45)
Low anterior resection	31 (36)	38 (45)
Abdominoperineal resection	9 (10)	6 (7)
Hartmann procedure	3 (3)	1 (1)
Other	1 (1)	1 (1)
Tumour stage*		
T1	4 (5)	3 (4)
T2	5 (6)	12 (15)
T3	71 (85)	65 (79)
T4	4 (5)	2 (2)
Nodal stage*		
N0	43 (51)	45 (55)
N1	13 (16)	15 (18)
N2	21 (25)	18 (22)
N3	7 (8)	4 (5)
Median (i.q.r.) height of tumour from anal verge (cm)	10 (7–14)	8 (6–13)
Adjuvant treatment		
Radiotherapy	4 (5)	6 (7)
Chemotherapy	11 (13)	16 (19)

Values in parentheses are percentages unless otherwise indicated. *Histopathological staging was not performed in four patients because of non-malignancy or resection not carried out. i.q.r., Interquartile range

abdominoperineal resection. Ten patients (12 per cent) in the laparoscopic group were converted to open resection (bleeding, three; excessive adhesions, four; anatomical uncertainty, one; technical difficulties, two). Three patients (3 per cent) in the laparoscopic group and one (1 per cent) in the open operation group underwent a Hartmann procedure. One patient in each group underwent formation of a defunctioning loop colostomy for locally advanced cancer. The majority of tumours were stage T3 (82 per cent). Two patients (one laparoscopic, one open operation) were subsequently discovered to have benign pathology on histological examination.

One hundred and eleven patients (65 per cent) were alive at the time of the survey, of whom 80 (72 per cent) responded to the postal questionnaire. The median interval between operation and questionnaire assessment was 3 (interquartile range (i.q.r.) 2–4) years. Among responders, there was an exact 50 per cent split, with 40 patients in each of the two groups.

Bladder function

Most patients had minimal urinary symptoms before operation, which was reflected in the median I-PSS score of 3 (i.q.r. 2–4) out of a possible score of 35. On follow-up there was no significant deterioration in median I-PSS symptom score in either the laparoscopic or the open group for men or women. Two patients in the laparoscopic group and none who had an open operation required long-term intermittent self-catheterization ($P = 0{\cdot}49$). One was a 57-year-old man who underwent abdominoperineal resection for a T3 N2 low rectal cancer, the other a 41-year-old woman who had low anterior resection for a T3 N1 tumour. Both had normal preoperative bladder function.

Sexual function

Of the 21 patients in the laparoscopic group who were sexually active before operation, the majority (15 of 21) were male. At a median of 3 years' follow-up, 16 of the 21 patients remained sexually active. The corresponding figures for patients having open operation were 28 (22 men) sexually active before operation, with 25 of the 28 patients remaining sexually active on follow-up. This reduction in sexual activity observed in the laparoscopic group was not statistically different from that observed for open operation ($P = 0{\cdot}26$, Fisher's exact test).

In the laparoscopic group, five of 15 men who were previously sexually active became impotent after operation, with a further patient reporting moderately impaired erectile function (*Table 2*). Among these five men, two had undergone a resection for a locally advanced rectal tumour (T3 N2), one had an abdominoperineal resection, one an ultra-low anterior resection, and the other a high anterior resection. In comparison, only one of 22 men in the open surgery group became impotent after operation, with two patients reporting a moderate impairment in erectile function. Similarly there was a significant difference between the two groups in terms of ejaculatory function, with six of 15 men in the laparoscopic group reporting inability to ejaculate after operation, compared with one of 22 in the open group. In the laparoscopic group, of the six men with inability to ejaculate, four were impotent, one had reduction in erectile function, and one had normal erection. In the open operation group, the only patient affected had both erectile and ejaculatory dysfunction. Hence, the overall rate of male sexual dysfunction after operation was seven of 15 in the laparoscopic group compared with one of 22 men having an open operation. This was reflected in the sexual satisfaction score, with a one-point median deterioration in the laparoscopic group, compared with no deterioration in the open group ($P = 0{\cdot}06$).

Six women in each group were sexually active before operation, and all but one in the open operation group remained sexually active on follow-up. One patient reported increased dyspareunia after the laparoscopic approach, but remained sexually active.

Discussion

The regulation of normal bladder and sexual function is dependent on an intact parasympathetic and sympathetic nerve supply. Sympathetic nerves emerge from the thoracic and lumbar spinal cord, synapse in the sympathetic ganglion, and send postganglionic hypogastric fibres to join the preganglionic parasympathetic nervi erigentes in the pelvic plexuses. It is along the pelvic side-walls and anteriorly where they enter their end-organs that these autonomic nerves are susceptible to injury during rectal resection. The pattern of injury depends not only on the extent of nerve trauma (e.g. unilateral *versus* bilateral), but also on the relative components of the autonomic supply injured, giving rise to variable symptoms of bladder and sexual dysfunction. In simple terms, the parasympathetic supply controls bladder contraction and normal erectile function, with injury resulting in detrusor areflexia and impotence, while the sympathetic supply controls bladder relaxation and ejaculation, with injury resulting in bladder instability and retrograde ejaculation or anejaculation.

The authors have attempted to document for the first time the rates of bladder and sexual dysfunction following laparoscopically assisted resection of rectal cancer and compared them with dysfunction following the conventional open operation. This was done by means of postal questionnaires sent to patients previously randomized within the context of a clinical trial. While postal questionnaires are subject to inherent biases, the authors consider their use to be justified when dealing with sensitive subject matter such as sexual and bladder function, especially when supported by telephone interviews[31]. The high response rate (72 per cent) achieved in this study minimized the effects of any response biases, which in any event should have been similar for both groups.

The incidence of bladder dysfunction was low following both laparoscopic and conventional open approaches, with no difference between the two groups in terms of change in median I-PSS scores. Only two patients (both in the laparoscopic group) reported significant bladder dysfunction necessitating intermittent catheterization, giving an overall incidence of 2·5 per cent. This value compares favourably with the findings in previous studies, which have reported the incidence of bladder denervation following rectal resection as ranging from 8 to 54 per cent[1–3]. Many of these earlier studies did not employ present-day techniques

Table 2 Male sexual dysfunction after resection of rectal cancer

	Laparoscopic approach (*n* = 15)	Open operation (*n* = 22)	*P*
Erectile function			0·03†
No difference	9	19	
Reduced	1	2	
Impotent	5	1	
Able to ejaculate			0·01†
Yes	9	21	
No	6	1	
Overall sexual dysfunction*	7	1	0·004†
Median (i.q.r.) change in sexual satisfaction	− 1 (− 3, 0)	0 (− 0·25, 0)	0·06‡

*Some patients were both impotent and unable to ejaculate. i.q.r., Interquartile range. †Fisher's exact test; ‡Mann–Whitney *U* test of TME. Since the introduction of TME and the recognized need for autonomic nerve preservation, the incidence of bladder complications appears to have diminished to a level of 0–4 per cent[7,16].

In comparison, sexual dysfunction remains a significant problem following rectal resection. This was particularly so for the 37 sexually active men in the present study, of whom eight experienced sexual dysfunction, compared with only one of 12 sexually active women. These figures compare favourably with those of older studies that reported rates of male impotence of 18–34 per cent and ejaculatory problems in 19–59 per cent[4–11], and are similar to recent studies utilizing TME in which impotence is reported as 11–25 per cent[15,16,32].

A significant difference in male sexual dysfunction was observed between the two groups. Interestingly, the rates of impotence and ejaculatory problems were similar, suggesting that both parasympathetic and sympathetic nerves are equally at risk of injury, and indicate that the most likely site of damage is at the lateral pelvic plexus where both autonomic systems converge.

As the stage of the tumours and the types of operation performed were similar between the two groups, the difference in sexual dysfunction must relate to technical differences between the two surgical approaches. It is accepted that laparoscopic surgery is technically more demanding than the open counterpart, and this is reflected in its protracted learning curve[18,25,33–35]. However, all the surgeons performing laparoscopically assisted rectal resection in the present study were experienced laparoscopic surgeons proficient in TME. The high incidence of sexual dysfunction in the laparoscopic group is particularly surprising given that completion of the rectal dissection and specimen delivery were in the main performed via a small suprapubic wound incision rather than by a totally intracorporeal technique. However, it should be noted that of the two patients requiring intermittent catheterization and the five patients with impotence in the laparoscopic group, all were operated on for either locally advanced cancers (T3 N1–2) or had low or abdominoperineal resections. The high incidence of bladder and sexual dysfunction therefore appears to be related to technical difficulties in resecting these particular types of tumour by means of a laparoscopic approach. This may be due to the increased difficulties in achieving adequate anterior rectal retraction within the confines of the male pelvis and a closed abdomen, particularly when the tumour is bulky or sited distally. However, as the rate of bladder denervation was low, the nerve damage must have occurred after the nerve to the bladder has branched off in the deep narrow pelvis of the male, where precise visualization and dissection may be more difficult. The proposed advantages of the laparoscopic technique, namely the improved visibility afforded by a magnified, well illuminated field of view, appear to be more than offset by these technical difficulties.

The high incidence of male sexual dysfunction translated into a significant difference in patient-reported satisfaction with sex life between the two groups. It is appreciated that the assessment of sexual function is a complex issue, dependent on both physical and psychological factors, with the definition of an adequate sex life varying from individual to individual. These difficulties are compounded in patients with rectal cancer, many of whom are elderly and not sexually active. However, the fact remains that the authors have observed an increased frequency of sexual dysfunction following laparoscopic resection. This fact should guide the surgical approach to this disease, particularly in sexually active males with bulky or low rectal cancers.

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Original article

Benefit of operative mortality reduction on colorectal cancer survival

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Background: The aim of this study was to determine trends in operative mortality after colorectal cancer surgery over a 20-year period in a well defined population, and consequences on overall survival.
Methods: Some 4745 new cases of colorectal adenocarcinoma were registered between 1976 and 1995 in a French region containing 500 000 people. Among these, 84·3 per cent were operated on, of whom 78·1 per cent were resected.
Results: The overall operative mortality rate decreased from 17·7 to 8·1 per cent between 1976–1979 and 1992–1995. Corresponding rates after curative surgery were 12·6 and 6·2 per cent respectively. Period of diagnosis, age and subsite were factors independently associated with operative mortality. Applying the operative mortality rates for the interval 1976–1979 to the 1992–1995 cohort, the expected 5-year survival rate after curative surgery would have been 40·0 per cent, compared with an observed rate of 51·0 per cent. This corresponds to a 27·5 per cent improvement in 5-year overall survival. Applying this result to the French population as a whole, it was estimated that almost 3000 deaths are avoided each year in France as a result of the reduction in operative mortality.
Conclusion: Operative mortality decreased dramatically over the 20 years of the study. It was associated with a significant improvement in survival after surgery for cure.

Presented to the 9th United European Gastroenterology Week, Amsterdam, The Netherlands, October 2001, and the European Cancer Conference 11, Lisbon, Portugal, October 2001; and published in abstract form as Gut 2001; **49**(Suppl III) and *Eur J Cancer* 2001; **37**(Suppl 6): 258
Paper accepted 23 July 2002 British Journal of Surgery 2002, **89**, 1557–1562

Introduction

With approximately 33 000 incident cases annually, colorectal cancer is the second most common type of cancer in women and the third in men in France[1]. Prognosis remains poor but improvement in survival has been reported recently in some European countries[1,2] and in the USA[3]. Improved diagnostic and therapeutic procedures have been put forward to explain survival trends as well as improvement in perioperative care[4]. As surgery remains the primary treatment for colorectal cancer, operative mortality represents an important problem. Most published data come from specialized surgical teams and as such their results cannot be used as a reference because of inevitable bias. Community-based studies that record all diagnosed cases in a well defined population seem to be the only way to assess real improvement in operative mortality in non-selected cases. Such studies are rare because they require accurate and detailed data collection which is seldom performed by general cancer registries. The purpose of this paper was to estimate trends in operative mortality after colorectal cancer surgery over a 20-year period in a well defined French population, and to assess their consequences on overall survival.

Patients and methods

A population-based registry of digestive tract cancers was established for the department of Côte-d'Or (Burgundy, France) in 1976. It covers a resident population of 493 931 inhabitants according to the 1990 census. Information is collected from public and private pathology laboratories, university and local hospitals, the regional cancer institute, private surgeons and gastroenterologists, general practitioners and death certificates. No cases were registered through death certificates alone, but these were used to

Table 1 Operative mortality according to interval of diagnosis

	1976–1979	1980–1983	1984–1987	1988–1991	1992–1995
Resection for cure	59 of 468 (12·6)	46 of 544 (8·5)	37 of 658 (5·6)	39 of 740 (5·3)	44 of 711 (6·2)
Palliative surgery	59 of 199 (29·6)	58 of 224 (25·9)	23 of 137 (16·8)	24 of 131 (18·3)	29 of 186 (15·6)
All cases	118 of 667 (17·7)	104 of 768 (13·5)	60 of 795 (7·5)	63 of 871 (7·2)	73 of 897 (8·1)

Values in parentheses are percentages

identify missing cases. Because of the involvement of the entire medical profession it was assumed that nearly all newly diagnosed cases were recorded. The quality and exhaustivity of the registry is certified every 4 years by an audit of the National Institute for Health and Medical Research.

A total of 4745 new cases of colorectal adenocarcinoma were registered between 1976 and 1995. Some 3998 patients (84·3 per cent) were operated on, of whom 3121 (78·1 per cent) were resected. For the present study, all the incident cases of colon and rectal cancer operated on were included. Colorectal cancers resected endoscopically or treated by laser therapy were excluded. The clinical history recorded for each patient included age at diagnosis, gender and date of diagnosis. Patients were categorized by age at diagnosis into three categories: aged under 60 years, aged between 60 and 74 years, and aged 75 years and above. Five 4-year time intervals were considered. Tumour location was classified according to the tenth revision of the International Classification of Diseases (ICD-10)[5] and regrouped into three anatomic subsites: the right colon consisted of the caecum (C18·0), appendix (C18·1), ascending colon (C18·2), hepatic flexure (C18·3) and transverse colon (C18·4); the left colon consisted of the splenic flexure (C18·5), descending colon (C18·6) and sigmoid colon (C18·7); and the rectum included the rectosigmoid junction (C19) and rectal ampulla (C20). Anal cancer cases (C21) were not included. Cancer extension at the time of diagnosis was classified for resected cancers according to the International Union Against Cancer[6]. Patients with visceral metastasis or those operated on without resection of the tumour were classified as having advanced-stage disease. Those who underwent resection but were not properly staged were classified as stage unknown. Surgical treatment was considered as curative when there was a macroscopic resection of all malignant tissue and no microscopic evidence of spread to the surgical margin. Operative mortality was defined as death within 30 days of surgery[7].

Associations between categorical data were analysed using χ^2 test for heterogeneity. A non-conditional logistic regression was used to obtain odds ratios associated with the probability of operative death for each interval adjusted for the other variables. The significance of co-variates was tested by the likelihood ratio test.

Survival was ascertained from the death certificate, the registrar of the place of birth or the medical practitioner. Seventeen patients (0·4 per cent) with an unknown status were excluded from the survival analysis. Relative survival was calculated, and was defined as the ratio of the observed survival rate to the expected survival rate in a particular area in a population of the same gender and age distribution as the cases estimated from population life tables. This provides an estimate of patient survival that is corrected for the effect of the causes of death. Relative survival was estimated for patients categorized by gender and period of diagnosis by means of a STATA© algorithm based on the methodology developed by Estève *et al.*[8].

The method described by Richards *et al.*[9] was used to estimate how many postoperative deaths were avoided among patients with cancer diagnosed between 1992 and 1995 as a result of their postoperative mortality rate being lower than that of patients diagnosed with cancer during the 1976–1979 interval. Avoided operative deaths were calculated as the difference between the observed and expected excess operative mortality. Predicted survival curves for a group of patients comparable to those of the 1992–1995 interval but with the operative mortality rate of the 1976–1979 interval were estimated. These rates were applied to the estimated number of new cases of colorectal cancer for the whole country, taking account of their distribution by age, sex and subsite. This extrapolation was justified by the fact that incidence[10] and survival rates[11] in the Côte d'Or area are similar to those estimated at the national level. All statistical tests were performed at the 0·05 level. The computations were performed using Stata Statistical software (Stata Corporation, College Station, Texas, USA).

Results

Overall operative mortality

Overall operative mortality rates decreased from 17·7 per cent between 1976 and 1979 to 7·5 per cent during the

Table 2 Operative mortality after curative surgery according to interval of diagnosis, gender, age at diagnosis, subsite and stage at diagnosis (univariate analysis)

	1976–1979	1980–1983	1984–1987	1988–1991	1992–1995	*P* for trend
Gender						0·66
Male	37 of 256 (14·5)	27 of 278 (9·7)	22 of 370 (5·9)	19 of 396 (4·8)	23 of 406 (5·7)	
Female	22 of 212 (10·4)	19 of 266 (7·1)	15 of 288 (5·2)	20 of 344 (5·8)	21 of 305 (6·9)	
Age (years)						< 0·001
< 60	5 of 91 (5·5)	2 of 106 (1·9)	1 of 127 (0·8)	2 of 132 (1·5)	0 of 117 (0)	
60–74	31 of 234 (13·2)	16 of 227 (7·0)	9 of 268 (3·4)	3 of 278 (1·1)	7 of 303 (2·3)	
≥ 75	23 of 143 (16·1)	28 of 211 (13·3)	27 of 263 (10·3)	34 of 330 (10·3)	37 of 291 (12·7)	
Subsite*						0·21
Right colon	12 of 96 (12·5)	17 of 139 (12·2)	15 of 179 (8·4)	17 of 230 (7·4)	19 of 211 (9·0)	
Left colon	25 of 149 (16·8)	16 of 195 (8·2)	15 of 254 (5·9)	10 of 244 (4·1)	13 of 211 (6·2)	
Rectum	22 of 223 (9·9)	13 of 210 (6·2)	7 of 225 (3·1)	12 of 265 (4·5)	12 of 289 (4·1)	
Stage†						0·75
I	12 of 97 (12·4)	10 of 129 (7·8)	9 of 138 (6·5)	5 of 161 (3·1)	10 of 198 (5·1)	
II	26 of 211 (12·3)	24 of 272 (8·8)	18 of 292 (6·2)	17 of 316 (5·4)	18 of 284 (6·3)	
III	21 of 159 (13·2)	11 of 132 (8·3)	9 of 210 (4·3)	16 of 239 (6·7)	15 of 211 (7·1)	
IV	0 of 1 (0)	0 of 10 (0)	1 of 17 (5·9)	1 of 23 (4·3)	1 of 18 (5·6)	

Values in parentheses are percentages. *Colon, NOS not presented (1 case, 0 operative death). †Stage unknown not presented (3 cases, 1 operative death)

interval 1984–1987. The rates remained stable over the subsequent 5-year periods (*Table 1*). Similar trends were observed for both curative surgery and palliative surgery. The operative mortality rate was two to three times higher after palliative surgery than after surgery for cure over the entire study period.

Operative mortality after surgery for cure

Operative mortality rates were not significantly different between men and women. Operative mortality rates increased with age, varying from 1·7 per cent for patients aged less than 60 years, 5·0 per cent for those aged 60–74 years, to 12·0 per cent for older patients ($P < 0{\cdot}001$). Operative mortality rates were also significantly associated with tumour location: 9·4 per cent for right colon cancer, 7·5 per cent for left colon cancer and 5·4 per cent for rectal cancer ($P = 0{\cdot}008$). Tumour stage was not associated with operative mortality. After curative surgery, operative mortality rates were 6·4 per cent for stage I tumours, 7·5 per cent for stage II and 7·6 per cent for stage III. Operative mortality rates by period and test for trend are represented in *Table 2*. There was a significant trend for operative mortality rates by age over the study period.

Interval of diagnosis, age and subsite were significant factors independently associated with operative mortality in the multivariate analysis (*Table 3*). The strongest factors associated with operative mortality were age at diagnosis (patients aged 75 years and over were eight times more likely than patients aged below 60 years to die in the postoperative period) and interval of diagnosis (the likelihood of postoperative death decreased threefold between the first and the last three intervals).

Table 3 Factors associated with operative mortality after curative surgery (multivariate analysis)

	Odds ratio
Interval	
1976–1979	1
1980–1983	0·53 (0·35, 0·81)
1984–1987	0·33 (0·21, 0·52)
1988–1991	0·29 (0·19, 0·45)
1992–1995	0·36 (0·24, 0·56)
Age (years)	
< 60	1
60–74	2·87 (1·46, 5·64)
≥ 75	8·06 (4·20, 15·49)
Subsite	
Right colon	1
Left colon	0·85 (0·61, 1·19)
Rectum	0·58 (0·40, 0·82)

Values in parentheses are 95 per cent confidence intervals

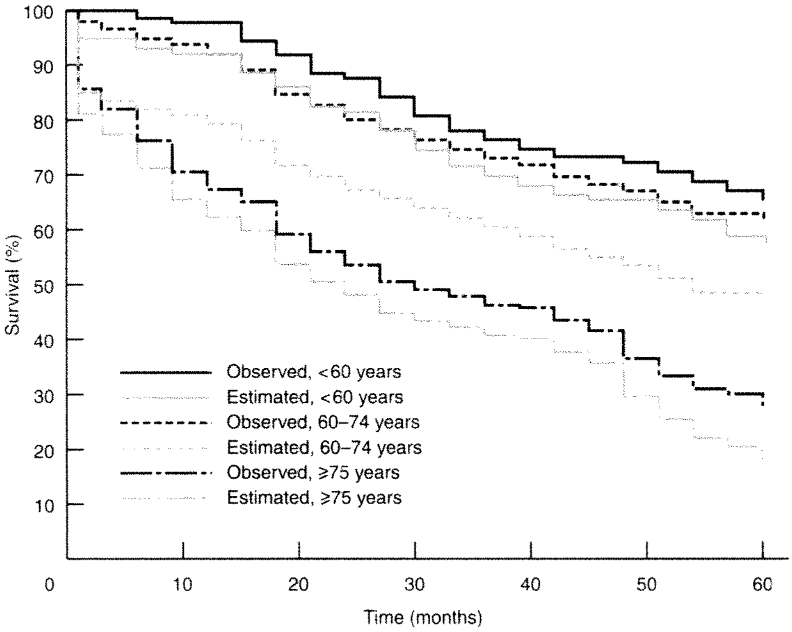
Estimated number of avoided deaths and improvement in survival in relation to reduction in operative mortality

Forty-four operative deaths were observed after curative surgery during the 1992–1995 interval compared with 93 expected operative deaths if there had been no improvement in operative mortality rate since the first interval studied.

Table 4 Observed and estimated 5-year survival rate after curative surgery for patients with cancer diagnosed during the interval 1992–1995 and deaths avoided owing to reduction of operative mortality compared with the interval 1976–1979

		Operative mortality rate (%)		Five-year survival rate (%)		
Age (years)	No. of patients*	1976–1979	1992–1995	Observed	Expected†	Relative reduction in deaths (%)
< 60	117	5·5	0	64·9 (55·6, 72·8)	55·8 (46·1, 64·5)	21·1
60–74	303	13·2	2·3	61·8 (56·0, 67·1)	46·9 (40·8, 52·8)	28·1
≥ 75	291	16·1	12·7	27·9 (22·6, 33·6)	17·5 (13·0, 22·5)	12·6

Values in parentheses are 95 per cent confidence intervals. *Seventeen patients with unknown status were excluded from the survival analysis. †Expected survival rate is the survival rate for patients with cancer diagnosed during the interval 1992–1995 but with the operative mortality rate for the interval 1976–1979



No. at risk	0	10	20	30	40	50	60
<60 years	117	110	100	90	81	68	41
60–74 years	303	280	250	228	209	168	88
≥75 years	286	208	176	152	138	94	53

Fig. 1 Observed and estimated survival curves after curative surgery by age for the interval 1992–1995

The estimated number of avoided deaths was therefore 49, corresponding to a relative reduction of 52 per cent in operative mortality rate.

Observed and estimated 5-year survival rates after curative surgery for patients with cancer diagnosed during the last study period are shown in *Table 4*. The reduction in operative mortality led to an estimated 21·1 per cent reduction in deaths within 5 years of diagnosis for patients aged under 60 years, 28·1 per cent for those aged between 60 and 74 years, and 12·6 per cent for patients aged 75 years and above. *Fig. 1* shows observed and predicted survival curves after curative surgery for the interval 1992–1995 by age group. The difference between observed and estimated survival curves enables survival improvement explained by the reduction in operative mortality to be estimated graphically. The biggest improvement was seen in the 60–74-year age group. The overall expected 5-year survival rate was 40·0 per cent whereas the overall observed 5-year survival rate was 51·0 per cent, corresponding to a 27·5 per cent relative improvement in the 5-year survival rate. Applying these results to the French population it was estimated that almost 3000 deaths are avoided each year in France because of the reduction in operative mortality rate (*Table 5*).

Table 5 Estimated number of deaths avoided 5 years after curative surgery for colorectal cancer in the French population

Age (years)	No. of patients*	Resection for cure (%)†	No. of patients resected for cure	No. of deaths avoided‡
< 60	6 850	78·7	5 391	491
60–74	14 515	73·5	10 671	1590
≥ 75	12 040	66·7	8 027	835

*Number of colorectal cancer incident cases in France in 1995 (FRANCIM). †Proportion of patients resected for cure for the interval 1992–1995 (Côte d'Or registry). ‡Difference between observed and estimated deaths within 5 years of diagnosis

Discussion

An important aspect of this study is to provide a non-biased estimation of trends in survival after surgery for colorectal cancer over a 20-year period in a non-selected population. There was a dramatic reduction in the overall operative mortality rate between the 1976–1979 period and 1984–1987 and subsequent intervals. As has already been reported, patients with advanced colorectal cancer treated with palliative surgery had a higher operative mortality rate than those with less advanced disease that was resected for cure. The striking trend in the reduction in operative mortality rate was seen both after surgery for cure and after palliative surgery.

Three factors were independently associated with operative mortality after surgery for cure in the multivariate analysis: age, interval of diagnosis and tumour location. Age at diagnosis was the main factor influencing operative mortality. The increase in operative mortality risk with advancing age is well known and is strongly associated with the presence of associated illness[12–16]. The reduction in operative mortality rate was particularly significant for patients aged under 75 years in the current study. This may be attributed to improved surgical technique but is probably due mainly to improvement in anaesthetic procedures, perioperative management and postoperative resuscitation[4,17]. The systematic use of antibiotics and mechanical bowel preparation has reduced the rate of postoperative sepsis. Monitoring, early nutritional support and systematic antithrombosis prophylaxis in the surgical intensive care unit during the postoperative period have also reduced the incidence of early postoperative complications[18,19]. Operative mortality was also related to tumour location; there were significantly more deaths after resection of right colon cancer. Emergency resection carries a twofold to fourfold increase in mortality rate because of the greater incidence of respiratory, cardiac and wound complications[20–22]. However, this does not explain the current findings as there were no more emergency resections for right than left colon cancer. The lower operative mortality rate after surgery for rectal cancer may be attributed to the fact that rectal cancer was more often treated in specialized centres with more experienced surgeons.

The principal observation in the study is that the decrease in operative mortality rate is a major reason for the improvement in overall survival observed over the 20 years of the study. Similar improvements in colorectal cancer survival have been reported in other European countries[1] and in the USA. A reduced postoperative mortality rate was the only likely explanation for the slight improvement in survival in two Swedish studies[2,4]. Other factors are involved in the improvement in colorectal cancer survival[23]. However, the current results suggest that the reduction in operative mortality plays a major role: the relative reduction of 52·0 per cent in operative death rate after curative surgery enabled the 5-year survival rate to improve by 27·5 per cent. These results should encourage aggressive management of patients with colorectal cancer.

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Preclinical studies of gene transfer for the treatment of desmoid disease in familial adenomatous polyposis

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Background Familial adenomatous polyposis (FAP) arises following mutation or loss of the adenomatous polyposis coli (*APC*) gene. Desmoid tumours are proliferations of fibroblasts and occur as an extracolonic manifestation of FAP. They are a leading cause of death after colectomy. The aim of this study was to assess the potential for *APC* gene transfer into fibroblasts *in vitro* and *in vivo* as a basis for consideration of gene therapy in the prevention or treatment of desmoid tumours.

Methods The *APC* gene was transferred by lipofection into fibroblasts in tissue culture and into peritoneum and small bowel mesentery *in vivo*. Reverse transcriptase–polymerase chain reaction was used to determine whether or not transfection was successful.

Results Transgene expression was recorded *in vitro* to 7 days after transfection. High levels of transgene expression were also seen in samples of peritoneum (all eight mice), small bowel mesentery (seven of eight), liver (seven of eight) and intestinal tissues (five to six of eight) following intraperitoneal treatment. Interestingly, transgene expression in gonadal tissues was occasionally noted.

Conclusion Liposomal transfection of *APC* gave prolonged high-level expression of the transgene, an important basis for gene therapy. No adverse effects were recorded. Further work is needed in animal models of desmoid disease to assess the clinical effects of gene therapy.

Paper accepted 23 July 2002

British Journal of Surgery 2002, 89, 1563–1569

Introduction

The hereditary condition familial adenomatous polyposis (FAP) is characterized by the development of hundreds to thousands of premalignant adenomatous polyps throughout the duodenum and colon. It is well known that both FAP and the majority of sporadic colorectal cancers arise following mutation or loss of the adenomatous polyposis coli (*APC*) gene[1–3]. However, germline mutations of this tumour suppressor gene not only cause intestinal polyposis, but are also linked to a variety of extraintestinal manifestations of disease, including potentially fatal desmoid tumours[4,5].

Desmoids are benign fibromatoses arising in musculoaponeurotic tissues. They can be aggressive in their infiltration and compression of surrounding structures, leading to considerable morbidity and even death. Desmoid disease is unusual in the general population but it affects approximately 10 per cent of patients with FAP; subclinical disease is present in an even greater percentage[5]. The majority of desmoids in FAP are intra-abdominal (70 per cent). Of these, 40–50 per cent arise in the mesentery[6,7] but some may arise from peritoneal fibroblasts.

Desmoids are a leading cause of morbidity and death in patients with FAP[8]. However, they pose difficult management decisions. Surgery provides temporary alleviation of local symptoms, especially for abdominal wall tumours, but intra-abdominal surgery for desmoids is hazardous and is thought to be an initiating factor in their development[7,9–11] so it is generally reserved for relief of obstruction or treatment of perforation. Radiotherapy may be beneficial in decreasing postoperative recurrence rates, especially in extra-abdominal disease[12,13]. However, radiosensitivity of the intestinal tract has limited its use for intra-abdominal desmoids. Medical treatment with non-steroidal anti-inflammatory drugs or oestrogenic compounds (such as tamoxifen) may be beneficial[14,15], and in some cases advanced disease has been treated effectively with combination cytotoxic chemotherapy[16,17]. However, chemotherapy has significant side-effects with no guarantee of cure or remission.

As it has been demonstrated that desmoids in FAP, like the intestinal adenomas, are clonal neoplasms arising from germline mutation or loss of one *APC* allele and somatic mutation or loss of the second allele[18–20], it is possible that corrective gene therapy could offer a new form of prophylaxis and/or treatment.

Previous studies have shown that the full-length human *APC* gene can be expressed in colonic epithelial cells[21] and in the rectal mucosa of wild-type and Min/+ mice, the latter being an animal model of FAP[22,23]. Indeed, a single enema treatment with *APC* in a liposomal vector has resulted in transgene expression for up to 21 days[24]. Therefore, this study has concentrated on lipofection as a means of *APC* gene transfer into fibroblasts *in vitro* and then into peritoneum and small bowel mesentery *in vivo*. Lipofection has been used as it is known to be safe and has shown a high transfection efficiency in this setting.

Materials and methods

Gene transfer

The *APC* gene construct contained full-length *APC*, from nucleotides −22 to + 8583, cloned into the pCMVβ-Neo-Bam vector. This was donated by the former Imperial Cancer Research Fund, and described in 1991 by Kinzler *et al.*[1,25]. Plasmid DNA was prepared as described previously[26] and complexed with the liposomal vector LipofectAMINE™ (Life Technologies, Gaithersburg, Maryland, USA) in the ratio 1 : 4 and 1 : 12 by weight for *in vitro* and *in vivo* studies respectively.

Cell culture and *in vitro* transfection

Fibroblasts used for the *in vitro* studies were primary cultures of human skin fibroblasts grown in-house under standard conditions. Transfection was performed using 1–2 mg DNA per well, each of which contained cells at 50–80 per cent confluence 24–48 h after plating out at a density of 1–3 × 10^5 cells per well. Negative controls using no DNA and no LipofectAMINE™ were included in each experiment. Following 5 h incubation with the liposomal complexes, 1 ml of growth medium containing twice the normal concentration of serum (Dulbecco's Modified Eagle Medium with 20 per cent fetal calf serum; Gibco™, Paisley, UK) was added to the cells. The medium was completely replaced 18–24 h later. The cells were harvested on days 1, 2, 3, 4 and 7 after transfection.

Gene transfer *in vivo*

All animal work was performed under the appropriate Home Office project and personal licences, with ethics committee approval. All mice used in this study were of the C57/BL6 strain, from which Min/+ mice have been derived. Eight mice were treated at 31 days of age by single intraperitoneal injection of the DNA–liposomal complex described above, containing 35 mg DNA and prepared to a final treatment volume of 250 ml with normal saline. Four littermates were used as controls and treated with a solution of LipofectAMINE™ alone, prepared in the same final volume. Following treatment all mice were observed for 20 min, then replaced in their cages and housed as normal. The treatment and control groups were housed in separate cages to prevent any inadvertent genetic contamination of the control animals via the faeco-oral route.

Two treated mice and one control mouse were killed on days 1, 2, 3 and 4, the day of treatment being termed day 0. Each mouse had an identical post-mortem examination to exclude the presence of free intraperitoneal fluid, intestinal distension or perforation. The liver, spleen, kidneys and pancreas were inspected, and any abnormality was recorded.

The liver, kidneys, gonads and samples of peritoneum were removed and snap-frozen in cryogenic tubes. The entire gastrointestinal tract was also removed. It was divided into stomach; small bowel sections one, two and three (numbered from proximal to distal small bowel in approximately equal sections); colon (as far as the splenic flexure); and rectosigmoid (everything distal to the splenic flexure). Each segment was opened longitudinally, washed in cold phosphate-buffered saline (Sigma-Aldrich, Saint Louis, Missouri, USA) and then frozen. All tissue samples were kept at −80°C until required.

Reverse transcriptase–polymerase chain reaction

Extraction and purification of messenger RNA (mRNA) was performed from cells and frozen tissue using standard methods (Quick Prep® Micro mRNA purification kit; Amersham Biosciences, Amersham, UK). The mRNA was converted to complementary DNA (cDNA) (First strand cDNA synthesis kit; Pharmacia) before amplification by the polymerase chain reaction (PCR) with Supertaq polymerase (HT Biotechnology, Cambridge, UK). All primers were purchased from Sigma-Genosys, Cambridge, UK. Those used here were 5′ GGA TCC TGA GAA CTT CAG 3′ (P1) and 5′ ATG CTT GTT CTG AGA TGA C 3′ (P2).

Primer P1 is complementary to a rabbit β-globin sequence of the plasmid just upstream of the *APC* insertion. Primer P2 spans part of the human *APC* sequence. Used together they amplify a 1396-base pair (bp) fragment with unspliced amplification and a 796-bp message following *in vivo* splicing[25]. Where the plasmid was taken into cells and transcribed, a band at either or both of these molecular

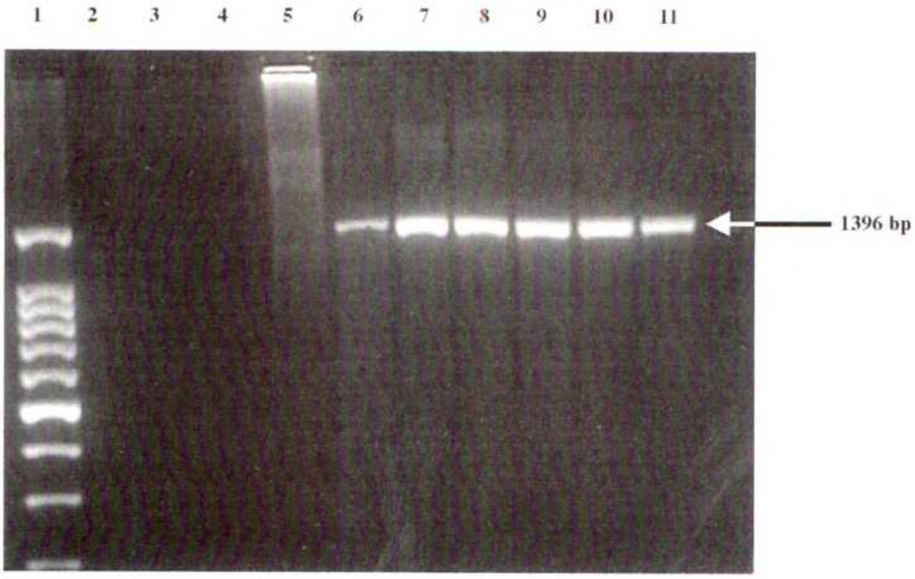


Fig. 1 Gel electrophoresis of fibroblast reverse transcriptase (RT)–polymerase chain reaction products 24 h to 7 days after transfection with the *APC* plasmid. Lane 1, 100-base pair (bp) marker (top band is 1500 bp); lane 2, empty; lane 3, no messenger RNA (mRNA); lane 4, no reverse transcriptase; lane 5, standard RNA; lane 6, no LipofectAMINE™; lane 7, day 1 fibroblast mRNA; lane 8, day 2 fibroblast mRNA; lane 9, day 3 fibroblast mRNA; lane 10, day 4 fibroblast mRNA; lane 11, day 7 fibroblast mRNA

weights was therefore expected. Appropriate positive and negative controls were included at all stages. *In vitro* these were no mRNA, no reverse transcriptase (RT), no LipofectAMINE™ and the inclusion of a standard cellular RNA control.

To ensure that absence of the appropriate PCR signal *in vivo* was due to lack of transgene expression and not simply technical error in tissue handling, a simultaneous control PCR reaction was run. An additional cDNA copy of each mRNA sample was amplified with primers for the ubiquitously expressed mouse β-actin. The primers MBAF (5′ CCC ATC TAC GAG GGC TAT GC 3′) and MBAR (5′ TTT GCT CCA ACC AAC TGC TG 3′) produced an 872-bp RT–PCR fragment.

Results

Transgene expression *in vitro*

The *APC* transgene persisted *in vitro* to 7 days after transfection (*Fig. 1*). The no RT control (*Fig. 1*, lane 4) was negative, indicating that the products were derived from the expressed transgene and not from contaminating plasmid sequences. There was a faint band in lane 6 (no LipofectAMINE™). This demonstrated that solitary plasmid DNA can enter fibroblasts *in vitro* and initiate transcription. However, the lipid vector enhances cellular uptake and transgene expression. Lane 5, containing standard cellular mRNA (from cells not involved in this experiment), did not show the specified sequence but there was a DNA smear indicating that the step conversion of mRNA to cDNA was successful.

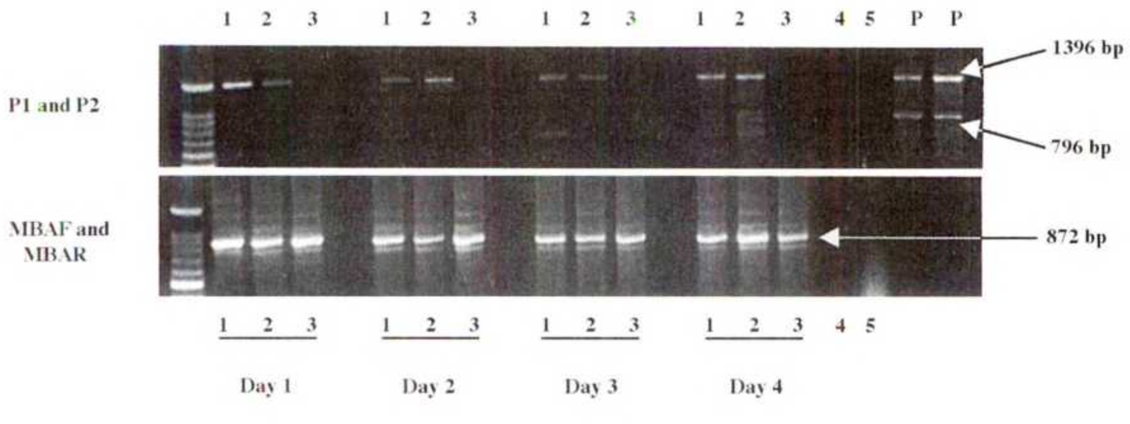
Transgene expression *in vivo*

Transgene expression *in vivo* was confirmed when two cDNA copies from an individual tissue sample gave a 1396-bp and/or 796-bp fragment following amplification with primers P1 and P2, in the presence of good negative controls (no signal in the no cDNA and no RT samples).

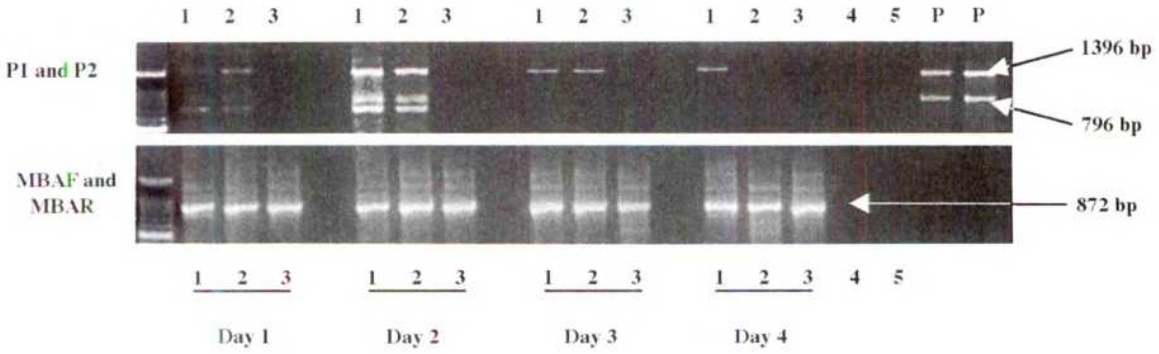
Transgene expression was excluded when no appropriately sized PCR product was generated from two cDNA copies of a tissue sample, in the presence of good positive controls (appropriately sized fragments generated from plasmid amplification with P1 and P2 and from matched cDNA amplified with MBAF and MBAR).

Peritoneal and mesenteric samples

All of the eight mice treated with *APC* pCMVβ-Neo-Bam expressed the transgene in the peritoneum, and only one mouse failed to express the exogenous mRNA in the small bowel mesentery. Both spliced and unspliced PCR products were seen in the mesentery, but only full-length mRNA was present in the peritoneal tissue. None of the mice treated with LipofectAMINE™ alone showed a positive band



a Peritoneal samples



b Mesenteric samples

Fig. 2 Agarose gel electrophoresis of reverse transcriptase (RT)–polymerase chain reaction products from **a** peritoneal and **b** mesenteric samples of all mice treated via the intraperitoneal route. The first lane on each gel is a 100-base pair (bp) DNA ladder, with bright bands at 500 and 1500 bp. Samples 1 and 2, mice treated with LipofectAMINE™ plus plasmid; sample 3, mouse treated with LipofectAMINE™ alone; sample 4, negative control (no RNA); sample 5, negative control (no RT); P, positive control (amplified plasmid complementary DNA)

(*Fig. 2* and *Table 1*). Peritoneal and mesenteric samples from all the mice (treated with plasmid or LipofectAMINE™ alone) expressed β-actin mRNA.

Intestinal tissues

Small bowel, colonic and rectosigmoid tissue samples taken from animals treated with *APC* pCMVβ-Neo-Bam showed a good level of transgene expression (over 65 per cent), with no obvious decrease in expression from the first to the fourth day after treatment (*Table 1*).

Liver and gonads

Transgene expression was seen in the liver of seven of the eight mice treated with the plasmid (*Table 1*). More than one-third of the mice treated with *APC* pCMVβ-Neo-Bam also showed transgene expression in the gonads (*Table 1*). All three of these mice were male.

Discussion

Loss or mutation of a tumour suppressor gene or mutation of a proto-oncogene initiates neoplasia. Corrective gene therapy aims to restore equilibrium in 'abnormal' cells with the administration of additional 'normal' copies of an affected tumour suppressor gene or by blockade of an affected oncogene. The majority of research to date has considered corrective gene therapy with wild-type *p53*, as this well characterized tumour suppressor gene is known to be mutated in a wide range of tumours. Indeed, proof of

Table 1 Sites of transgene expression in individual animals after intraperitoneal treatment with *APC* pCMVβ-Neo-Bam

	Peritoneum	Mesentery	Liver	Gonads	Small bowel	Colon	Rectosigmoid
Day 1							
Mouse 1	+	+		+		+	
Mouse 2	+	+	+		+		+
Day 2							
Mouse 4	+	+	+		+	+	
Mouse 5	+	+	+	+	+	+	+
Day 3							
Mouse 7	+	+	+	+		+	
Mouse 8	+	+	+		+	+	+
Day 4							
Mouse 10	+	+	+			+	+
Mouse 11	+		+		+		+

Animals treated with LipofectAMINE™ alone consistently tested negative for exogenous messenger RNA

principle studies with *p53* gene therapy have clearly demonstrated the benefit of corrective gene therapy in cellular systems, animal models of lung cancer and human lung disease[27,28].

Given that FAP desmoids are clonal tumours carrying an *APC* mutation, corrective gene therapy with 'normal' *APC* may be a way to 'stabilize' the at-risk connective tissue (such as the small bowel mesentery and peritoneum) that appears prone to tumour formation following stressful interventions such as surgery. It could be administered on a regular basis in high-risk families or around the time of surgery in others with classical FAP.

To date, virus-mediated gene therapy has been the main focus of attention owing to its ability to provide good transfection efficacy. However, in the light of a recent death following an adverse immune reaction to an adenoviral vector[29], and concerns surrounding the possibility of recombination events in all viral vectors, interest in safe non-viral methods of gene delivery has been rekindled. Liposomes are the most widely used non-viral gene vectors, and have already proved useful in clinical trials of cancer[30] and cystic fibrosis[31] gene therapy. The large DNA-carrying capacity of liposomes is also an advantage when considering the transport of a large gene, such as *APC*.

The plasmid used in this project contained the *APC* cDNA construct cloned into a CMVβ-Neo-Bam vector. This plasmid has several useful features. It is a relatively small plasmid, allowing large pieces of DNA to be cloned into it while still being of manageable size. It also replicates to a high copy number in transformed bacteria and carries two antibiotic resistance genes that can be used as selectable markers. Its cytomegalovirus promoter initiates high-level transcription in a wide range of cell types. The plasmid purification and amplification processes utilized here gave good quantities of pure product, as described previously[26].

Fibroblasts cultured from skin biopsies from patients with FAP show defective organization of cytoplasmic actin, similar to that seen in desmoid tumours. They also have morphological abnormalities and increased susceptibility to viral transformation. These observations support the hypothesis that FAP-associated desmoids arise through abnormal fibroblast proliferation in the presence of an *APC* mutation[5]. Given this degree of similarity between skin fibroblasts and desmoids, it is likely that the prolonged *APC* gene expression in fibroblasts demonstrated here could be used as a basis for gene transfer into desmoid cell lines if and when these become available.

Intraperitoneal chemotherapy has been widely used alone and in combination with intravenous agents in the adjuvant treatment of ovarian cancer[32]. There have also been occasional reports of its use in the management of peritoneal metastases from other origins, such as appendiceal or colorectal tumours[33]. Treatment is generally administered at intervals over a prolonged period, through an intraperitoneal catheter. The time taken for the drug to cross the peritoneum into the circulation means that high doses of chemotherapeutic agents can be administered locally into the peritoneal cavity and moderate doses are delivered slowly to the systemic circulation without a toxic peak[34].

Intraperitoneal gene therapy is a step on from intraperitoneal chemotherapy. Cytotoxic gene therapy has been delivered in this way in animal models of pancreatic carcinomatosis, in which the transgene was taken up and expressed preferentially in tumour cells[35], possibly owing to an increased proliferation rate[36]. Intraperitoneal administration of corrective gene therapy using *p53*-liposome complexes has also been used in a mouse model of residual glioblastoma; good levels of tumour transfection and cell death were seen[37]. However, neither of these studies recorded transgene expression in 'normal' tissues within the abdominal cavity.

The present study clearly demonstrates prolonged *APC* transgene expression in benign mesentery and peritoneum following a single intraperitoneal treatment. Taken to its extreme, this may allow the expression of wild-type *APC* in preneoplastic lesions in an attempt to prevent the initial development of desmoids. However, even if neoplastic change had commenced, the increased rate of proliferation seen in locally aggressive disease might itself enhance transgene expression in affected cells and slow or even reverse the disease process[38].

The next step in evaluation of intraperitoneal *APC* gene therapy as a means of treatment for desmoids would be to extend the period between treatment and tissue collection, and then to examine the effect of treatment in an animal model of desmoid disease. The most commonly used is the Apc1638N mouse. Unfortunately, however, this has largely musculoskeletal desmoids rather than intra-abdominal disease.

Intraperitoneal administration of wild-type *APC* is also a potential means of delivering intestinal gene therapy in FAP. Indeed, five to six of eight mice treated with the plasmid expressed the transgene in the small bowel, colon and rectosigmoid. However, RT–PCR was performed on sections of whole bowel in the treated animals and it was not clear whether transgene expression was confined to the serosa or reached the mucosa, where its effect might be beneficial. Mucosal stripping and RT–PCR of just this segment of bowel would be useful in future experiments to address this issue. Prolonged or repeated intraperitoneal administration of gene therapy in Min/+ mice could also be attempted to record the clinical effects of such treatment on intestinal disease.

The high level of transgene expression seen in the liver (seven of eight *APC*-treated mice) was probably due to a local effect of transfection into superficial hepatocytes. However, simultaneous delivery of small quantities of the DNA–liposome complexes into the systemic circulation may also have been responsible as this has previously been shown to lead to low-level hepatocellular expression of transgene[39,40].

Interestingly, transgene expression was seen in gonadal samples of three male mice treated with intraperitoneal *APC* pCMVβ-Neo-Bam. It is possible that the treatment initiated a rise in intra-abdominal pressure, allowing fluid to move directly through a patent processus vaginalis and come into contact with the testes. Alternatively, gonadal expression could have been secondary to systemic circulation of the complex. The over-representation of transgene expression in male mice might lead one to prefer the former explanation; however, only two of the eight mice treated with the plasmid were female so the likelihood of seeing gonadal expression in a female was low. If intraperitoneal gene therapy were to be used in the management of human disease further studies of gonadal expression would be needed so that adequate advice could be given to patients.

Overall the level of transgene expression in fibroblasts *in vitro* and in all tissues following intraperitoneal gene therapy was higher than might have been expected. This is a method of *APC* gene therapy that requires more extensive investigation, particularly in relation to its use in the prevention and management of desmoid disease.

Acknowledgements

The authors are grateful to Dr Harpreet Wasan and colleagues at the Imperial Cancer Research Fund for the use of the Min/+ colonies. This work was supported by a BJS Research Bursary. R.M.B.-T. is supported by Research Training Fellowships from the Royal College of Surgeons of England and the Digestive Disorders Foundation and Alimentary Pharmacology and Therapeutics Trust.

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Short note

Double-blind placebo-controlled crossover study of sacral nerve stimulation for idiopathic constipation

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Paper accepted 23 July 2002

Introduction

Constipation is common, causing decreased bowel frequency, difficulty in evacuation, abdominal pain and bloating. Organic and drug-associated causes account for a minority of cases. Initial dietary and pharmacological therapies are often unsuccessful, particularly in the long term, and are not without side-effects. Behavioural therapy will improve a majority of patients, but many remain symptomatic. If conservative treatment fails, surgical options include either a bowel resection or a stoma. Subtotal colectomy with ileorectal anastomosis is the most widely performed procedure, but has a high failure rate and associated morbidity. A colostomy may relieve symptoms but it is an unattractive option for most patients, and abdominal pain and bloating may persist.

An alternative approach involves modifying the neural control of the lower bowel and pelvic floor through sacral nerve stimulation. This technique, established in the treatment of detrusor irritability and urinary retention, has more recently been used successfully to treat resistant faecal incontinence[1]. Two reports of temporary stimulation for constipation have shown symptomatic improvement[2,3] and the only report of permanent stimulation showed a sustained symptomatic benefit in three of four patients[4].

It is possible that this benefit relates to a placebo effect. The efficacy of this treatment was therefore evaluated in a double-blind crossover trial.

Patients and methods

Two women, aged 36 years, with severe resistant idiopathic constipation who were implanted with a permanent stimulator 12 months previously were studied. The time between implantation and this study ensured that medium-term clinical benefit was maintained and optimal stimulation parameters had been determined.

Before implantation of the stimulator both women had failed maximal conservative treatment and were considered psychologically stable. Both had a normal sigmoidoscopy, whole-gut transit time was prolonged and proctography showed delayed evacuation with no other significant abnormality. Ethics committee approval and informed consent were obtained.

The technique for sacral nerve stimulation has been described previously[5]. Both patients had a successful 3-week trial of percutaneous stimulation before one-stage permanent implantation of a stimulator to the S3 foramen.

The study consisted of two 2-week intervals with subsensory stimulation either 'on' or 'off'. The patient and investigator were blinded. A bowel diary, the Wexner constipation score, a symptom analogue score, anorectal physiological testing and quality of life assessment were performed at baseline and after each interval.

Results

There was a marked difference in bowel frequencies, the percentage time with abdominal pain and bloating, and the symptom analogue score when the stimulator was 'on' compared with 'off'. These differences were similar to the differences between baseline pretreatment and at 1 year of permanent stimulation. Symptoms returned rapidly to baseline levels without stimulation. The results of anorectal physiological testing were inconclusive (*Table 1*). The Short Form 36 quality of life questionnaire showed a marked improvement in both patients after a year of chronic stimulation compared with baseline. There were no complications and both patients rapidly regained their clinical benefit once stimulation was reinstated.

Discussion

It is rare in surgery to be able to perform a double-blind placebo-controlled crossover evaluation. Stimulation below the sensory threshold made this possible. In normal clinical use stimulation levels vary, but are often just within the sensory range, so that the patient is reassured that the device is functioning.

This study demonstrates that chronic sacral nerve stimulation for idiopathic constipation can produce a clinical benefit with an increased bowel frequency at 1 year after implantation. There was an associated improvement in symptoms of abdominal pain and bloating, overall satisfaction and quality of life scores. Transit time was not measured as the authors have previously demonstrated no change in transit time, despite symptomatic improvement in one study[3], and a variable effect in another[4].

Once the stimulation was removed the clinical benefit was lost, and symptoms rapidly returned to baseline levels. As the study was blinded this suggests that there is no placebo effect, mirroring previous experience in faecal incontinence. It is also apparent that constant stimulation is required to elicit clinical benefit, and that temporary

Table 1 Clinical and physiological results

	Patient 1				Patient 2			
	Baseline	1 year	Stimulation off	Stimulation on	Baseline	1 year	Stimulation off	Stimulation on
Bowel frequency (per 2 weeks)	1	15	2	10	6	17	4	8
Time with pain and bloating (%)	95	0	65	0	100	0	93	65
Wexner constipation score (0–30)	22	4	15	5	20	6	13	13
Symptom analogue score (0–100)	32	94	30	88	28	84	33	60
Anal resting pressure (cmH_2O) ($N > 60$)	65	82	63	68	84	87	39	84
Anal squeeze pressure (cm H_2O) ($N > 60$)	32	52	51	41	46	104	57	145
Threshold sensation (ml air) ($N < 45$)	45	20	30	20	47	60	40	15
Urge sensation (ml air) ($N < 90$)	185	35	60	33	75	75	80	35
Maximum volume (ml air) ($N < 190$)	245	65	85	65	143	100	120	70
Anal electrosensation (mA) (2–9·4)	5·6	4·8	5·4	5·2	7·2	6·0	6·6	5·4
Rectal electrosensation (mA) (7–36)	29·0	13·0	14·5	19·0	16·2	15·0	26·0	12·0

Bowel frequency is the number of episodes of defaecation in a 2-week diary period. Resting pressure is the maximal anal resting pressure using a stationary pull-through technique. Squeeze pressure is the maximal increment above resting pressure. Threshold, urge and maximal tolerated volume are to rectal balloon distension with air. Anal and rectal electrosensation are threshold sensation with increasing amplitude of stimulation, recorded with a 1-cm bipolar ring electrode (5 Hz, 0·1 ms and 10 Hz, 0·5 ms respectively)

treatment may have no long-lasting effects. The rapid reversal of symptoms after 1 year of chronic stimulation suggests that a rapidly reversibly, neurologically mediated mechanism is involved, rather than chronic changes in pelvic floor musculature.

Changes in anorectal physiological variables were inconclusive; however, in treating constipation, either altered visceral hindgut function or rectoanal coordination is likely to play an important role.

The numbers in this study were small. However, there are very few patients who have had sacral nerve stimulators for constipation implanted for long enough, and who use subsensory stimulation, to undergo this type of assessment. Future studies of longer duration with larger patient numbers are now required to confirm the findings.

Acknowledgements

Financial support has been received from Medtronic, Minneapolis, Minnesota, USA. However, the study design, performance, analysis and reporting has been conducted without the influence of Medtronic.

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Original article

Allopurinol and superoxide dismutase protect against leucocyte–endothelium interactions in a novel model of colonic ischaemia–reperfusion

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Background: Leucocyte recruitment is a key feature in ischaemia–reperfusion (I/R)-triggered tissue injury. However, the mechanisms underlying leucocyte–endothelium interactions in the large bowel remain elusive because of a previous lack of models to examine the colonic microcirculation. The aim of this study was to develop and validate a novel method for studying reperfusion-induced leucocyte–endothelium interactions in the colon.

Methods: The superior mesenteric artery was occluded for 30 min in male C57/Bl6 mice and leucocyte responses were analysed in colonic venules after 30–240 min of reperfusion. Analysis of leucocyte rolling and adhesion in colonic venules was made possible by an inverted approach using intravital fluorescence microscopy.

Results: Thirty minutes of ischaemia and 120 min of reperfusion induced the strongest and most reproducible increase in leucocyte rolling and adhesion. This was associated with a significant increase in colonic levels of malondialdehyde (MDA). Administration of allopurinol and superoxide dismutase reduced I/R-induced leucocyte responses in a dose-dependent manner. Pretreatment with allopurinol attenuated the tissue content MDA in the colon by more than 60 per cent.

Conclusion: A new method for examining I/R-induced leucocyte responses in the colonic microcirculation is described. Oxygen free radicals play an important role in triggering leucocyte rolling and adhesion in colonic venules.

Paper accepted 23 July 2002

British Journal of Surgery 2002, 89, 1572–1580

Introduction

Reperfusion of ischaemic tissues is associated with enhanced production of oxygen radicals, endothelial barrier dysfunction and tissue injury. A rate-limiting step in the pathophysiology of ischaemia–reperfusion (I/R) damage is the activation and recruitment of leucocytes[1,2]. Numerous studies have demonstrated that leucocyte accumulation is a multistep process, which is initiated by a rolling adhesive interaction followed by activation and firm adhesion of leucocytes to the endothelium in postcapillary venules[1,2]. Leucocyte rolling reduces the velocity and allows time for leucocytes to detect chemotactic signals on the endothelial surface. It is now widely accepted that leucocyte rolling is a precondition for the subsequent firm adhesion and extravascular accumulation[3,4]. By use of intravital microscopy, several studies have demonstrated that leucocyte rolling is predominantly mediated by the selectin family of adhesion molecules and that stationary adhesion is supported by the β_2-integrins[1,2].

Gut ischaemia is frequently encountered in trauma, strangulated bowel, cardiovascular surgery and haemorrhagic shock[5]. In this context, it is noteworthy that most intravital microscopic studies of I/R-induced leucocyte–endothelium interactions in the gastrointestinal tract have mainly been restricted to observations in the small bowel[6–8] because of a lack of experimental models with which to

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

examine adhesive leucocyte–endothelium responses in the large bowel. However, substantial morphological and functional differences exist between the small and large intestine. For example, it has been shown that the colon is markedly less susceptible to ischaemia than the small bowel[9]. Moreover, the bacterial load in the colon is more extensive than that in the small intestine and, considering the important role assigned to endotoxins produced by enteric bacteria in splanchnic I/R[10], it is conceivable that specific characteristics in the time course, magnitude and mechanisms of leucocyte recruitment may prevail in the large bowel. In addition, specific adhesion molecules exhibit distinct and overlapping functions in various organs, and their expression appears to depend on the nature of the proinflammatory stimulus. All these differences underline the importance of studying individual microvascular beds in order to understand organ-specific characteristics of postischaemic leucocyte responses and tissue damage.

Oxygen free radicals (OFRs) are intimately involved in the inflammatory cascade and have been shown to activate leucocytes, induce lipid peroxidation and increase microvascular permeability[11,12]. In a variety of different models, administration of superoxide dismutase (SOD) and catalase has been shown to protect against I/R-induced tissue injury by enhanced metabolism of OFRs[9,11]. Another way to protect from OFR-induced organ damage is by pretreatment with allopurinol, which inhibits xanthine oxidase-mediated production of OFRs[11]. Their ability to reduce tissue levels of OFRs makes allopurinol and SOD suitable for validating the pathophysiological role of OFRs in models of I/R.

Based on these considerations, the aim of the present study was to develop and validate a new model for studying I/R-induced leucocyte rolling and adhesion in the colonic microcirculation *in vivo*. For this purpose, an inverted fluorescence microscope was adapted for intravital assessment of leucocyte responses in the mouse colon. The role of OFRs in reperfusion-induced inflammation in the colon was examined by use of allopurinol and SOD.

Materials and methods

Animals

Male C57/Bl6 mice weighing 22–26 g were kept under standard laboratory conditions. Animals were maintained on a 12-h light and 12-h dark cycle and were allowed free access to animal chow and tap water. All experimental procedures were approved by the Regional Ethical Committee for Animal Experimentation.

Anaesthetic and surgical preparation

The mice were anaesthetized with 7·5 mg ketamine hydrochloride (Hoffman-La Roche, Basel, Switzerland) and 2·5 mg xylazine (Janssen Pharmaceutica, Beerse, Belgium) per 100 g body-weight by intraperitoneal injection. The animals were placed in the supine position on a heating pad (37°C) for maintenance of body temperature. A polyethylene catheter (internal diameter of 0·28 mm) was placed into the internal jugular vein for administration of test substances and fluorescent markers. A midline laparotomy was performed and the abdominal contents were deflected to the left side. The aorta and the vena cava were identified along with the coeliac axis and the superior mesenteric artery (SMA). A non-traumatic vascular clamp was placed carefully across the SMA at the aortic origin in order to induce gut ischaemia. The major portion of the colonic blood supply is supplied by the SMA in rats[13].

Experimental protocol

The animals were divided into groups. Sham-operated mice ($n = 6$) that underwent laparotomy but not I/R served as negative controls. The other groups of mice underwent 30 min of ischaemia and leucocyte–endothelium interactions were analysed after indicated periods (30, 60, 120 and 240 min) of reperfusion ($n = 6$–8 in each group). To examine the role of OFRs in I/R in the colon, mice were pretreated with allopurinol (Sigma Chemical, St Louis, Missouri, USA) and SOD (Sigma Chemical). Allopurinol (0·1–10 mg per kg per day; $n = 6$) was administered intraperitoneally for 5 days before experimentation. SOD (15–15 000 units/kg; $n = 5$–6) was injected intravenously immediately before reperfusion. Animals that underwent I/R, but had phosphate-buffered saline (PBS) treatment only ($n = 8$), served as positive controls. At the end of the experiments, blood samples were obtained from the internal jugular vein for analysis of systemic leucocyte differential counts.

Lipid peroxidation

The colonic content of malondialdehyde (MDA) was determined as an index of lipid peroxidation. Lipid peroxidation is a well known mechanism of OFR-induced cellular injury and is used as an indicator of oxidative stress in cells and tissues[14,15]. Lipid peroxides are unstable and decompose to form a complex series of compounds. Polyunsaturated fatty acid peroxides generate MDA and 4-hydroxyalkenals upon decomposition. LPO-586™ (R & D Europe, Abingdon, UK) is a colorimetric assay designed to quantify MDA and is based on the reaction of a chromogenic reagent, *N*-methyl-2-phenylindole, with MDA at 45°C. One molecule of MDA reacts with two molecules of *N*-methyl-2-phenylindole to yield a stable chromophore with maximal absorbance at 586 nm. Colonic tissues were collected, washed with ice-cold PBS and homogenized in phosphate buffer 20 mmol/l (pH 7·4) and butylated hydroxytoluene 0·5 mol/l. An aliquot (200 µl) of the homogenate was added to a reaction mixture containing 650 µl *N*-methyl-2-phenylindole and 150 µl hydrochloric acid 12 mol/l. The samples were incubated in a water bath for 60 min at 45°C and centrifuged at 15 000g for 10 min. The absorbance of the supernatant was measured by spectrophotometry at 586 nm.

Intravital microscopy

The colonic microcirculation was observed using an inverted Olympus microscope (IX70; Olympus Optical, Hamburg, Germany) equipped with different lenses (× 10/numerical aperture 0·25 and × 40/numerical aperture 0·60). The microscopic images were televised using a charge-coupled device video camera (FK 6990 Cohu; Pieper, Schwerte, Germany) and recorded on videotape for subsequent off-line analysis. After positioning under the microscope, a 5-min equilibration period preceded quantitative measurements. Analysis of leucocyte–endothelium interactions (rolling and adhesion) was made in venules (inner diameter 15–30 µm) in the submucosa (beyond longitudinal and circular muscle capillaries) with stable resting blood flow. Blood perfusion within individual microvessels was studied after contrast enhancement by intravenous administration of fluorescein isothiocyanate-labelled dextran (0·05 ml, 5 mg/ml; Sigma Chemical). *In vivo* labelling of leucocytes with rhodamine-6G (0·1 ml, 0·5 mg/ml; Sigma Chemical) enabled quantitative analysis of leucocyte flow behaviour in the colonic microcirculation. Quantification of microcirculatory variables was performed off-line by frame-to-frame analysis of the videotaped images. Leucocyte rolling was determined by counting the number of leucocytes passing a reference point in the venule per 20 s and is expressed as cells per minute. Firm adhesion was measured by counting the number of cells adhering to the venular endothelium (segments 200–300 µm long) and remaining stationary for 20 s, and is given as cells per millimetre venule length. Blood flow velocities were measured off-line by use of CapImage® software (Zeintl, Heidelberg, Germany). CapImage® is a computer-based video image analysis system for quantification of microvascular dynamics, such as vessel diameters, capillary density and erythrocyte flow velocity[16]. The erythrocyte flow velocity was determined by using the line shift method, the spatial correlation method and the auto flying spot method[16]. The velocity was calculated as a mean value from five to eight measurements per venule and is expressed as millimetres per second. Venular wall shear rate was determined based on the Newtonian definition as 8((red blood cell velocity/1·6)/venular diameter) as described previously[17].

Histology

A 0·5-cm long segment of the distal colon was fixed overnight in 4 per cent formaldehyde and embedded in paraffin for histological analysis. The colon sections were stained with haematoxylin and eosin and analysed under light microscopy.

Systemic leucocyte counts

Some 20 µl blood was mixed with Turk's solution (0·2 mg gentian violet in 1 ml glacial acetic acid, 6·25 per cent v/v) at a 1 : 10 dilution. Leucocytes were counted and differentiated as polymorphonuclear or mononuclear cells in a Burker chamber.

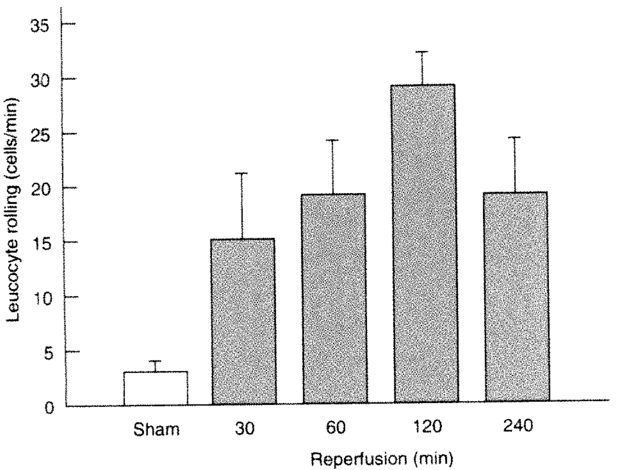
Statistical analysis

Statistical evaluations were performed using the Kruskal–Wallis one-way analysis of variance on ranks for unpaired samples (Dunn's post-hoc test was used). The results are presented as mean(s.e.m.). Differences were considered to be significant at $P < 0·05$.

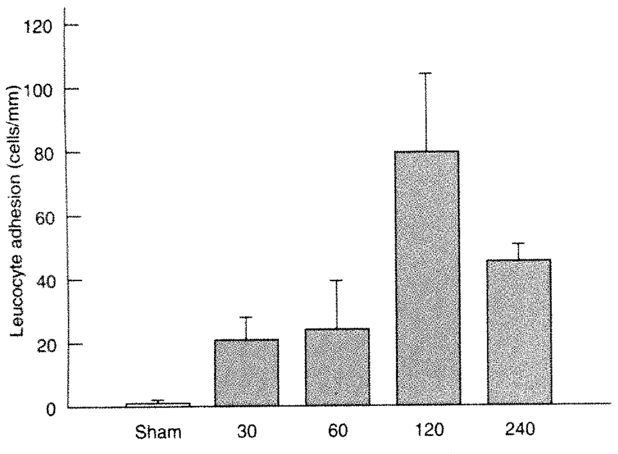
Results

Ischaemia–reperfusion-induced leucocyte–endothelium interactions in the colon

Baseline observations of leucocyte rolling and adhesion in negative control mice (sham operated) revealed only occasional interactions between leucocytes and the microvascular endothelium; the number of rolling and adherent leucocytes was 3·0(1·4) cells/min and 0·8(0·7) cells/mm respectively ($n = 6$) (*Fig. 1*). I/R markedly increased both leucocyte rolling and firm adhesion. An ischaemic period of 30 min followed by 120 min of reperfusion produced the greatest and most reproducible leucocyte responses: leucocyte rolling and adhesion were 24·7(3·4) cells/min and 74·8(24·6) cells/mm respectively ($n = 6–8$; $P < 0·05$ *versus* sham) (*Fig. 1*). Occlusion of the SMA caused a significant reduction in capillary perfusion (more than 85 per cent of the capillaries in the colon were non-perfused after clamping the SMA). Longer periods of ischaemia, i.e. 60, 75 and 90 min, followed by 60 or 120 min of reperfusion

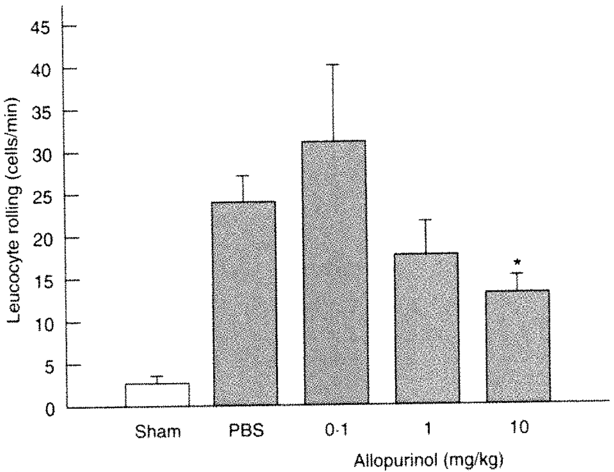


a Rolling

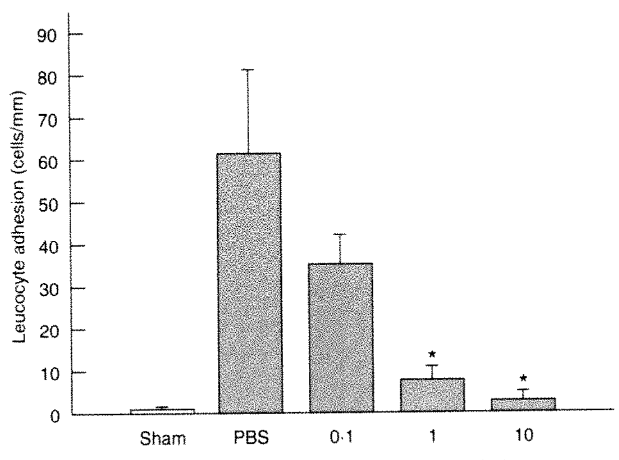


b Adherence

Fig. 1 Mean(s.e.m.) venular leucocyte **a** rolling and **b** adhesion in the mouse colon after 30 min of ischaemia and 30–240 min of reperfusion. Sham-operated animals served as negative controls (open bar)



a Rolling



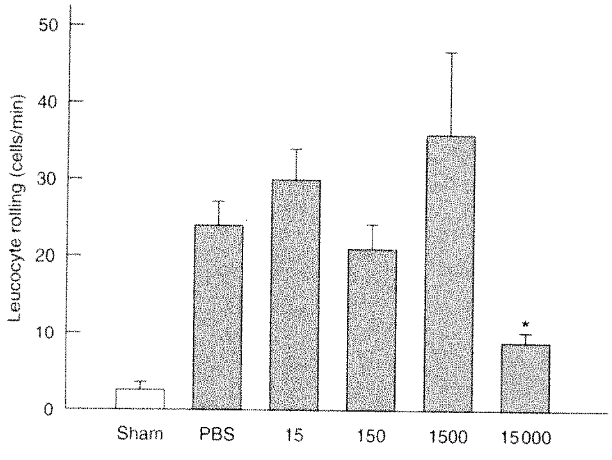
b Adherence

Fig. 2 Mean(s.e.m.) venular leucocyte **a** rolling and **b** adhesion in the mouse colon after 30 min of ischaemia and 120 min of reperfusion. Sham-operated animals served as negative controls (open bar). Mice were pretreated with allopurinol (0·1–10 mg/kg) for 5 days and positive controls received phosphate-buffered saline (PBS). $^{*}P < 0{\cdot}05$ *versus* PBS (n = 6–8) (Kruskal–Wallis test)

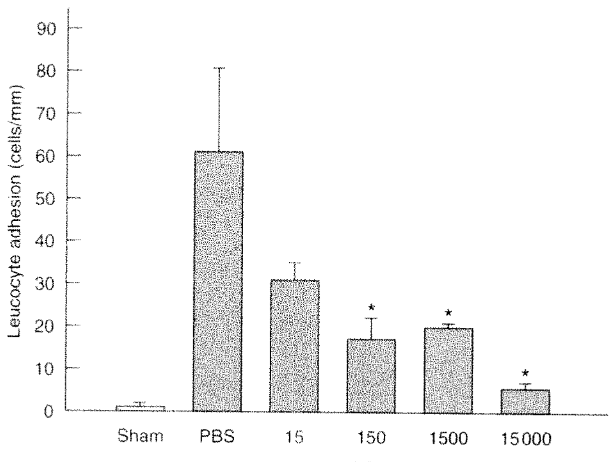
were associated with a higher mortality rate, and a less marked and reproducible leucocyte response (data not shown). Although reperfusion periods of 30, 60 and 240 min also produced an increase in the number of rolling and adherent leucocytes, the peak response occurred at 120 min of reperfusion (*Fig. 1*). Thirty minutes of ischaemia and 120 min of reperfusion was therefore applied in all further experiments.

Role of oxygen free radicals in ischaemia–reperfusion-induced leucocyte response

To evaluate the role of OFRs in I/R-induced leucocyte–endothelium interactions, allopurinol and SOD were used[9,11]. Allopurinol (0·1–10 mg/kg) reduced leucocyte rolling and adhesion in a dose-dependent manner (n = 6; $P < 0{\cdot}05$ *versus* PBS) (*Fig. 2*). At all doses of allopurinol used the effect on firm adhesion was more pronounced than that on leucocyte rolling. Pretreatment of mice with SOD (15–15 000 units/kg) immediately before reperfusion attenuated reperfusion-induced leucocyte–endothelium interactions in a dose-dependent fashion (*Fig. 3*). However, only the highest concentration of SOD (15 000 units/kg) had the capacity to significantly reduce leucocyte rolling (n = 5; $P < 0{\cdot}05$ *versus* PBS). On the other hand, SOD



a Rolling



b Adherence

Fig. 3 Mean(s.e.m.) venular leucocyte **a** rolling and **b** adhesion in the mouse colon after 30 min of ischaemia and 120 min of reperfusion. Sham-operated animals served as negative controls (open bar). Mice were pretreated with superoxide dismutase (SOD) (15–15 000 units/kg) immediately before reperfusion and positive controls received phosphate-buffered saline (PBS). $^*P < 0{\cdot}05$ *versus* PBS ($n = 5$–8) (Kruskal–Wallis test)

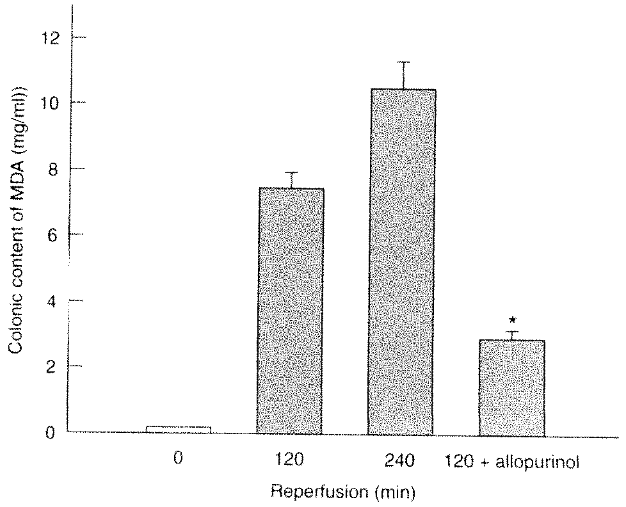


Fig. 4 Mean(s.e.m.) levels of malondialdehyde (MDA) in the mouse colon after 30 min of ischaemia and 120 or 240 min of reperfusion. Sham-operated animals served as negative controls (open bar). In separate experiments, mice were pretreated with allopurinol 10 mg/kg for 5 days. $^*P < 0{\cdot}05$ *versus* 120 ($n = 5$) (Kruskal–Wallis test)

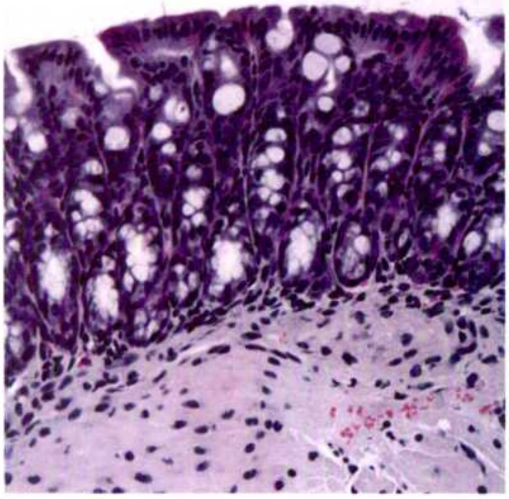
potently inhibited firm adhesion of leucocytes to the microvascular endothelium.

Reperfusion of ischaemic colon caused a substantial increase in the colonic MDA concentration ($n = 5$; $P < 0{\cdot}05$ *versus* sham) (*Fig. 4*). Pretreatment with allopurinol 10 mg/kg significantly reduced tissue MDA levels after I/R (*Fig. 4*) ($n = 5$; $P < 0{\cdot}05$ *versus* PBS), indicating a key role of OFRs in this experimental model.

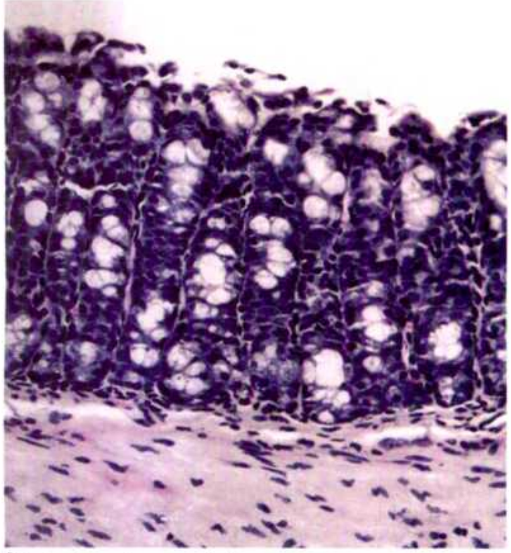
Histological examination of colonic specimens demonstrated normal architecture of the colon in sham-operated mice (*Fig. 5a*). Thirty minutes of ischaemia and 120 min of reperfusion caused only minor structural changes, such as mucosal damage (*Fig. 5b*). Colonic microcirculation, demonstrated by use of inverted intravital microscopy after 30 min of ischaemia and 120 min of reperfusion, is shown in *Fig. 6*. No significant differences in systemic leucocyte differentials (*Table 1*) or haemodynamic variables (*Table 2*) were identified between the experimental groups.

Discussion

Mechanistic studies of microcirculatory and leucocyte responses associated with reperfusion of the intestine have predominately been restricted to investigations in the small bowel[6–8] because of a lack of appropriate *in vivo* models adapted for direct observations in the large bowel. In the present study, a novel approach to examining mechanisms regulating postischaemic leucocyte responses and perfusion failure in the colon is described. In this context, it is important to note that there are several important differences between the small and large bowel. For example, the number of bacteria in the colon is much larger than that in the small bowel. This confers an important role to the colonic epithelium in sustaining a physical barrier against translocation of pathogenic bacteria and absorption of noxious substances[18]. Moreover, epithelial cell turnover and metabolic rate are higher in the small intestine than the colon[19], so oxygen consumption is greater in the small



a Control



b Ischaemia–reperfusion

Fig. 5 Sections of colon from **a** sham-operated controls and **b** mice that underwent 30 min of ischaemia and 120 min of reperfusion. Ischaemia–reperfusion induced distinct mucosal damage and cell infiltration. (Haematoxylin and eosin stain, original magnification × 200)

bowel and may increase its sensitivity to hypoxia. Leung *et al.*[9] have reported that the small intestine is substantially more susceptible to I/R injury than the colon. Considering the aforementioned differences, it is conceivable that specific characteristics in the time course, magnitude and mechanisms of the acute inflammatory response may exist in the large bowel. Study of individual microvascular beds in order to understand organ-specific characteristics of postischaemic leucocyte responses and tissue damage is warranted.

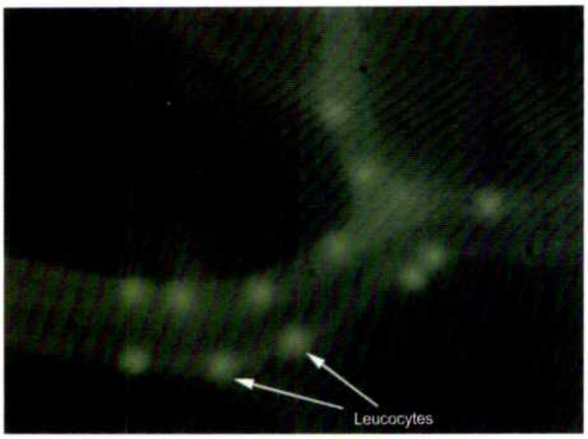


Fig. 6 Intravital microscopy of the colonic microcirculation illustrating a postcapillary venule in the colonic submucosa after 30 min of ischaemia and 120 min of reperfusion with numerous leucocytes interacting with the endothelial lining

Numerous investigations have demonstrated that recruitment of leucocytes is a rate-limiting step in the pathophysiology of I/R[1,2]. Activated leucocytes release tissue-damaging products, such as OFRs and proteases that cause organ dysfunction[20]. In the present study 30 min of ischaemia and 120 min of reperfusion produced the strongest and most reproducible leucocyte response. A clear-cut increase in leucocyte rolling and adhesion was observed at 30 min of reperfusion, which peaked at 120 min and returned towards baseline values after 240 min. Longer periods of ischaemia caused increased mortality and elicited less consistent changes in leucocyte rolling and adhesion, suggesting that ischaemia for 30 min is optimal for mechanistic studies of reperfusion-induced leucocyte–endothelium interactions in the large bowel. Moreover, morphological examination of the colon revealed inflammatory cell infiltration and mucosal damage, in line with previous histological observations of early reperfusion injury in the colon[9,21].

Generation of OFRs is a key component in the pathogenesis of I/R-induced tissue damage in the gastrointestinal tract[6–8,12,22]. Lipid peroxidation is a well established mechanism of cell injury and a useful indicator of oxidative stress[12,14]. In the present study production of MDA, a product of lipid peroxidation[15], was analysed. Tissue MDA was markedly increased after 30 min of ischaemia followed by 120 or 240 min of reperfusion, indicating a substantial yield of OFR-induced damage in the colonic model of I/R. Pretreatment with the xanthine oxidase inhibitor allopurinol significantly attenuated gener-

Table 1 Systemic leucocyte differential counts

	Polymorphonuclear cells ($\times 10^6$ cells/ml)	Mononuclear cells ($\times 10^6$ cells/ml)	Total ($\times 10^6$ cells/ml)
Sham	1·1(0·1)	3·3(0·3)	4·4(0·3)
Positive control	1·5(0·1)	3·9(0·3)	4·5(0·4)
Allopurinol (mg/kg)			
0·1	1·4(0·4)	3·4(0·4)	4·8(0·9)
1	1·5(0·3)	4·9(0·3)	6·4(0·4)
10	0·8(0·1)	4·9(0·3)	5·7(0·3)
Superoxide dismutase (units/kg)			
15	1·7(0·2)	4·7(0·3)	6·3(0·3)
150	1·9(0·3)	5·4(0·6)	7·2(0·8)
1500	1·4(0·1)	3·4(0·2)	4·7(0·3)
15 000	0·9(0·1)	2·7(0·2)	3·6(0·2)

Values are mean(s.e.m.). Ischaemia was induced by clamping the superior mesenteric artery (SMA) for 30 min followed by 120 min of reperfusion. Sham-operated controls underwent identical procedures except clamping of the SMA ($n = 6$). Animals were pretreated with allopurinol for 5 days ($n = 6$) or superoxide dismutase ($n = 5$–6) and positive controls received phosphate-buffered saline ($n = 8$). Blood was collected from the internal jugular vein after the experiments

Table 2 Haemodynamic variables in colonic venules

	Diameter (µm)	Red blood cell velocity (mm s^{-1})	Wall shear rate (s^{-1})
Sham	21·0(2·1)	0·84(0·15)	291(44)
Positive control	24·2(1·2)	1·25(0·12)	264(19)
Allopurinol (mg/kg)			
0·1	19·2(0·1)	1·01(0·13)	251(39)
1	23·0(1·1)	0·95(0·11)	205(50)
10	20·2(1·6)	0·84(0·12)	222(38)
Superoxide dismutase (units/kg)			
15	19·8(1·4)	0·95(0·14)	194(42)
150	21·0(1·3)	0·99(0·13)	180(31)
1500	20·6(0·6)	0·76(0·07)	185(34)
15 000	21·0(1·5)	1·03(0·12)	210(46)

Values are mean(s.e.m.). Ischaemia was induced by clamping the superior mesenteric artery (SMA) for 30 min followed by 120 min of reperfusion. Sham-operated controls underwent identical procedures except clamping of the SMA ($n = 6$). Animals were pretreated with allopurinol for 5 days ($n = 6$) or superoxide dismutase ($n = 5$–6) and positive controls received phosphate-buffered saline ($n = 8$)

ation of colonic MDA in response to this I/R insult, suggesting that allopurinol reduced the production of OFRs in the large bowel. Questions about the importance of xanthine oxidase in reperfusion-provoked injury in the colon have been raised in the literature, based on the finding that the content of xanthine oxidase in the large intestine is relatively low. In fact, the colonic levels of xanthine oxidase appear to be less than one tenth of those in the small intestine under normal conditions[9]. None the less, the current data suggest that xanthine oxidase-generated OFRs also play an important role in I/R-induced leucocyte recruitment in the large bowel.

Based on the known ability of exogenously administered SOD to protect organ function in experimental models of I/R, it is widely accepted that superoxide has a fundamental role in microvascular dysfunction and accumulation of leucocytes associated with reperfusion of ischaemic tissues[11,23]. Pretreatment with SOD significantly reduced reperfusion-induced leucocyte rolling and adhesion, suggesting that superoxide is also involved in the recruitment of inflammatory cells in colonic I/R. This supports the hypothesis that the colon, like small bowel, mesentery, liver, skin and striated muscle, is protected from reperfusion-induced OFR generation and leucocyte accumulation by allopurinol and SOD[11,23–26], and validates the importance of OFR formation in this model of I/R in the colon.

It is interesting to note that low doses of allopurinol and SOD, which had no effect on the frequency of rolling leucocytes, still markedly reduced the number of firmly adherent leucocytes. These observations suggest that firm leucocyte adhesion is more sensitive to inhibition of OFR generation (i.e. allopurinol and SOD pretreatment) than leucocyte rolling. Leucocyte rolling is more easily triggered than firm adhesion and is a precondition to subsequent firm adhesion[3,4]. For example, gentle and non-traumatic exteriorization of tissues is associated with a clear-cut and rapid induction of leucocyte rolling whereas leucocyte adhesion is usually absent or rare[3,4,27]. Thus, the remaining OFRs after administration of lower doses of allopurinol and SOD may be sufficient to provoke leucocyte rolling but not stationary adhesion of leucocytes along the microvascular endothelium. An important link between I/R and leucocyte rolling has been highlighted by previous studies which demonstrated that OFRs rapidly and potently increase the expression of P-selectin on endothelial cells[28,29]. Indeed, several studies have documented that leucocyte rolling is predominately supported by P-selectin in non-lymphoid tissues[4,30,31].

There are alternative techniques for studying the microcirculation *in vivo*. Orthogonal polarization spectral (OPS) imaging can provide images of the microcirculation similar to those achieved with intravital microscopy[32,33], although there are important differences between these two techniques. One difference is that OPS imaging is mainly restricted to observations of microvascular haemodynamics, i.e. blood flow and vessel diameters, whereas intravital microscopy, which allows the use of fluorescent dyes, provides clear-cut visualization of leucocyte/platelet–endothelium interactions[34]. Moreover, plasma leakage and apoptosis (nuclear condensation and fragmentation) can be quantified using intravital microscopy with fluorescent dyes[11,35]. When interpreting data from OPS imaging it should be noted that the microvascular diameters are systematically 2–5 μm smaller than values obtained from intravital microscopy. This is related to technical properties of OPS imaging, which detects only red blood cells and not the plasma gap adjacent to the endothelial lining[33].

In conclusion, the present study describes a novel technique for examining the mechanisms that regulate I/R-induced leucocyte–endothelium interactions in the colonic microcirculation. OFRs are generated in this model of I/R and inhibition of OFR production attenuates postischaemic leucocyte rolling and firm adhesion in colonic venules. This new model may provide an important instrument with which to identify therapeutic targets to control pathological recruitment of inflammatory cells associated with I/R injury in the colon.

Acknowledgements

This study was supported financially by the Swedish Medical Research Council (K2000-04P-13411-01A, K2002-73-X-14273-01A), Crafoordska stiftelsen (20010968), Direktör Albert Påhlssons stiftelse för välgörenhet och forskning, Harald och Greta Jaenssons stiftelse, Greta och Johan Kocks stiftelser, Einar och Inga Nilssons stiftelse, Nanna Swartz stiftelse, Ruth och Rickard Julins stiftelse, Svenska Läkaresällskapet (2001-907), Allmäna sjukhusets i Malmö stiftelse för bekämpande av cancer, MAS fonder. A.A.R. is supported by a European Surgical Research Fellowship from the Royal College of Surgeons of England.

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Original article

Karyotypic aberrations of chromosomes 16 and 17 are related to survival in patients with breast cancer

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Background: Breast cancer has a high incidence and associated mortality rate, yet little is known of the sequence of genetic events that underlie the clinical course.

Methods: The study was a comparative genomic hybridization analysis of 40 primary breast cancers with survival data at a mean of 8·4 years.

Results: The mean number of aberrations was 9·0, with a mean of 5·5 gains and 3·5 deletions per tumour. The most common aberrations were: gain of 1q (27 of 40), 8q (19 of 40) and 17q (13 of 40), and deletion of 17p (12 of 40) and 8p (11 of 40). These results are consistent with a distinctive pattern of large-scale (karyotypic) genetic change in primary breast cancer.

Conclusion: The novel findings of this study were that only women who were disease-free had loss of 16q (E-cadherin) in association with a gain of 16p, and 17p13 (*p53*) loss combined with 17q12 (*HER2*) amplification was found only in the cancers of women who developed recurrent disease. The karyotypic changes seen in primary breast cancer seem to be associated with outcome and point to the underlying genetic events.

Presented in part to the British Cancer Research Meeting, Leeds, UK, July 2001 and the Nottingham International Breast Cancer Conference, Nottingham, UK, September 2001
Paper accepted 13 July 2002
British Journal of Surgery 2002, **89**, 1581–1586

Introduction

Breast cancer affects one in 12 women in the western world and is predicted to increase in incidence[1]. Little is known about the molecular basis of breast cancer progression and clinical behaviour. It has been suggested that the biological behaviour of breast cancers is dictated by their specific pattern of genetic abnormalities[2]. In clinical practice, oestrogen receptor (ER) expression[3] and amplification of *HER2*[4] inform patient management, but the main prognostic indicators remain tumour size, tumour grade and node status[5]. There is a need to explore the underlying molecular events in breast cancer.

Comparative genomic hybridization (CGH) is a technique that allows the whole genome of a test sample to be analysed for amplifications or deletions by comparison with normal reference DNA[6,7]. A deleted region must be at least 5 Mb to be detectable, but high-level amplifications of as little as 50 kb have been detected[8]. Chromosomal changes such as these have been shown to occur in many malignant solid tumours[9], and CGH may identify linked patterns of copy number changes peculiar to a histological subtype. Furthermore, by observing several tumours with a deletion or amplification on the same chromosome arm, CGH can identify a minimum region of overlap (MRO). These MROs represent targets for more detailed molecular analysis. However, as gains and losses are measured in relation to the ratio of test : reference DNA, balanced translocations and ploidy changes are not detected.

CGH has been used previously to study breast cancer[7,10–14]. All of these reports found amplifications of 1q and 8q to be among the most common amplifications, and generally 8p and 17p were the regions most commonly deleted. Indeed, these were among the most common aberrations when the data for 27 different solid tumour types were pooled[9].

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Using CGH, Roylance *et al.*[15] found that the proportion of grade 1 tumours displaying loss of 16q was greater than the proportion of grade 3 tumours showing loss of the same region; they reasoned that, as regain of genetic material is extremely unlikely, grade 1 tumours do not develop into grade 3 tumours. Agreement was found between these data and subsequent allelic imbalance analysis[16]. Support for this argument is the finding that primary and metastatic breast cancers are usually of the same grade[17]. Also, losses of 16q material were found almost exclusively in well and intermediately differentiated ductal carcinoma *in situ* (DCIS)[18], and a higher frequency of 17q12 amplifications in poorly differentiated DCIS, indicating that the different species of tumour are defined early in development rather than as a tumour becomes metastatic. Further analysis of this series of 57 tumours[19] revealed that losses of 16q correlated with conventional indicators of good prognosis (low mitotic index and apoptotic index, and absence of necrosis), whereas the presence of a 17q gain correlated with poor prognostic indicators (high mitotic and apoptotic indices, and presence of necrosis). The presence of an amplification of 20q13, which may be an indicator of poor clinical outcome[10], and of 11q13 has been associated with disease recurrence[20]. These data support the hypothesis that the genetic events during carcinogenesis dictate the subsequent behaviour of the breast cancer. However, to date, the implications of karyotypic events in the tumour on disease behaviour have not been clear.

The aim of this study was to use CGH to analyse 40 previously untreated primary breast tumours for karyotypic DNA copy number changes in order to identify amplifications and deletions that might be related to prognostic features and patient outcome.

Patients and methods

Samples

Samples of histologically confirmed primary tumour tissue were obtained from 40 women who underwent surgical resection, snap-frozen in liquid nitrogen and stored at −80°C. Tumours were selected from consecutive patients where there was material for research in excess of that required for clinical diagnosis and staging. Of the 40 women, 22 were histologically axillary node positive and 20 were ER positive. Twenty women subsequently developed recurrent breast cancer, 18 of whom died from the disease during follow-up (minimum 7 years; mean 8 years 4 months). Ethical approval was obtained for the study.

DNA extraction

DNA was extracted from tumour tissue by phenol extraction. A shaving (approximately 5 × 5 mm) of tissue was digested with proteinase K overnight at 55°C. Two rounds of phenol extraction were followed by DNA precipitation with isopropanol and ethanol washes. The DNA pellet was air-dried and dissolved in water. Reference (normal) DNA was extracted from the lymphocytes of unrelated individuals using a Nucleon™ BACC2 kit (Amersham Biosciences, Little Chalfont, UK), following the manufacturer's protocol.

Preparation of metaphase spreads

Slides of cells in metaphase were prepared according to standard laboratory procedure. Briefly, blood was cultured for 72 h in the presence of phytohaemaglutinin to stimulate lymphocyte division. After 48 h, cells were blocked by adding thymidine to the medium. The block was removed 4 h before harvest. Demicolcine was added, and after 10 min the cells were spun down and resuspended in fixative (3 : 1 methanol : acetic acid). After three changes of fixative, cells were dropped on to slides and allowed to dry.

Comparative genomic hybridization

Using a nick translation kit (Vysis, Richmond, UK), DNA was fluorochrome-labelled by nick translation in the presence of either Spectrum Green™ 2′-deoxyuridine 5′-triphosphate (dUTP) (tumour DNA) or Spectrum Red™ dUTP (reference DNA) (Abbott Laboratories, Maidenhead, UK). Probe size was between 500 and 2000 bp, as determined by electrophoresis.

A probe mix containing 400 ng test DNA, 400 ng reference DNA and 10 µg unlabelled human *COT1* DNA was precipitated with sodium acetate and cold ethanol, and centrifuged. The pellet was dried and redissolved in 10 µl Hybrisol VII® buffer (Appligene Oncor Lifescreen, Watford, UK). A standard metaphase spread was denatured with 70 per cent formamide, the probe mix applied and sealed under a coverslip with rubber solution glue. Hybridization was carried out for 72 h at 37°C in a humidified chamber. Unhybridized probe was removed with two washes of saline sodium citrate buffer/nonidet-P40 (Amersham Biosciences), and the chromosomes were counterstained with 4,6-diamino-2-phenyl-indole in anti-fade solution (Appligene, Harefield, UK).

For each sample, at least eight metaphase spreads were captured using an epifluorescence microscope (Olympus® BX60, Olympus Optical, Southall, UK) equipped with three single excitation filters, a multibandpass emission filter, dichroic mirror and a cooled charge-coupled device camera. Images were collected and analysed using Vysis Quips™ (Abbott Laboratories) software on a MacIntosh® G3 computer (Apple®, Cupertino, California, USA). Losses of genetic material were deemed to have occurred where the green : red fluorescence ratio was below 0·8 and amplification where the ratio exceeded 1·2. These limits are more extreme than the ratio changes of 0·85–1·15 documented for normal : normal hybridizations[7]. A copy number change involving both arms of a chromosome was considered to be two events. When the profile returned to a green : red ratio of 1·0 between copy number changes on the same chromosome arm, this was considered as two events. As test and reference DNAs were not sex matched, data for the X-chromosome were not included.

Statistical analysis

Numbers of aberrations in different outcome groups were compared with the Wilcoxon rank sum test. Associations between individual aberrations and outcome were analysed using Fisher's exact test (two tailed).

Results

For the whole group of 40 breast tumours, the mean number of amplifications was 5·5 (range 0–15), the mean number of deletions was 3·5 (range 0–15) and the mean number of aberrations (gains and losses) was 9·0 (range 0–28). Three tumours showed no detectable copy number changes.

The MROs of the most common amplifications were 1q32 and 1q23-24, 3q26.2-26.3, 8q23, 10p13, 16p13.1, 17q22, 18q21, 20q12-ter. For deletions, the MROs were 1p35-36.1, 8p21-22, 11q14-22, 16q22-23, 17p13, 19p13.3. Thus the most common regions of amplification were 1q (in 27 of the 40 tumours), 8q (in 19 of 40) and 17q (in 13 of 40), while 17p (12 of 40), 8p (11 of 40) and 19p (10 of 40) were most commonly deleted (*Fig. 1*).

Nine tumours had amplifications with no deletions, but only two had deletions with no amplifications. The regions most commonly amplified where no deletion was present were 1q, 16p and 17q. The only aberrations appearing alone were a 1q amplification (one tumour) and a 17q21-23 amplification (one tumour).

The number of deletions per tumour in the group of patients who died or had disease recurrence was significantly greater than the number among those who were alive and disease-free at follow-up ($P = 0{\cdot}025$, Wilcoxon rank sum test) (*Table 1*). There were no significant differences for amplifications or number of aberrations per patient. The three patients with no detectable copy number change were alive without disease recurrence.

In examining the relationship between specific aberrations and outcome, deletions of 17p were significantly more common among node-positive women (ten of 22) than among node-negative women (two of 18) ($P = 0{\cdot}035$, Fisher's exact test). This was reflected in the difference between the numbers with 17p deletion in the group with breast cancer recurrence (eight of 20) and the group with no recurrence (four of 20), although it was not statistically

Table 1 Relationship between disease behaviour, comparative genomic hybridization abnormalities, and clinical or pathological features in 40 women treated for breast cancer, grouped according to recurrence

	Recurrent disease (*n* = 20)	Alive, no recurrence (*n* = 20)
Mean no. of aberrations	10·15	7·85
Mean no. of deletions	4·50	2·55*
Mean no. of amplifications	5·65	5·30
Oestrogen receptor positive	9	11
Node positive	16	6
Mean (range) tumour size (cm)	3·05 (1–4)	2·35 (2–4)

*$P = 0{\cdot}025$ *versus* recurrent disease (Wilcoxon rank sum test)

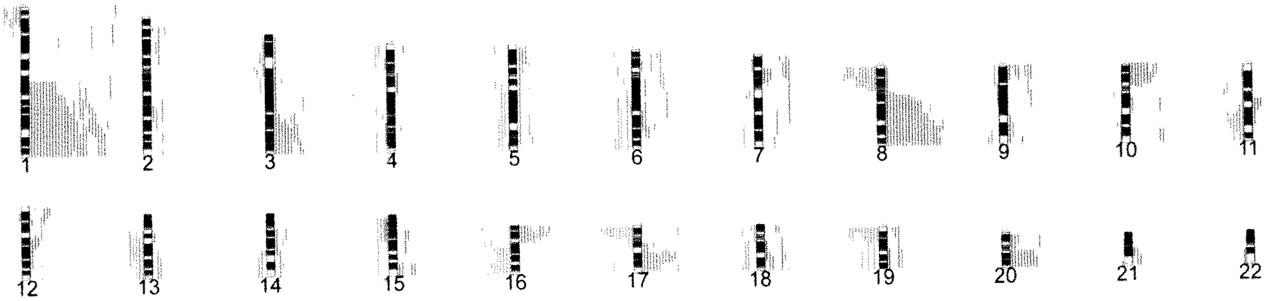


Fig. 1 Comparative genomic hybridization results of 40 breast carcinomas. Chromosomes are numbered 1–22 (X-chromosome omitted). Red bars to the left of each chromosome indicate regions of chromosomal deletion; common deletions included 8p, 16q, 17p and 19p. Green bars to the right of each chromosome show regions of amplification; most common gains were 1q, 8q, 10p, 16p, 17q and 20q

significant. In addition, eight of 20 tumours from women who were alive and well at follow-up had a gain of 16p with loss of 16q, while none of the 20 recurrent tumours had this combination ($P = 0{\cdot}002$, Fisher's exact test) (*Fig. 2*).

Discussion

By means of CGH, this study has identified karyotypic abnormalities in 37 of 40 breast cancers, demonstrating that multiple abnormalities are associated with poor outcome; 17p deletions were particularly associated with axillary node positivity. The study confirmed that amplifications of 1q and 8q and deletions of 8p and 17p are consistent, common aberrations in breast cancer[7,10–14]. Several other sites of amplification and deletion have been mentioned in previous reports, but these were not found consistently.

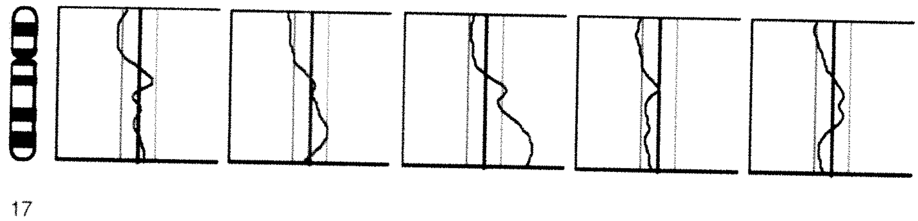
The significant association between a higher mean number of deletions per tumour and outcome (4·70 in patients who died during follow-up *versus* 2·55 in survivors), rather than an association with amplification, concurs with previously published evidence[10].

Several aberrations identified here, such as 17q[15,21,22] and 20q[10,15,22,23] amplification, have previously been correlated with poor outcome, but there was no evidence in the present study that 11q amplification was a poor prognostic marker[20].

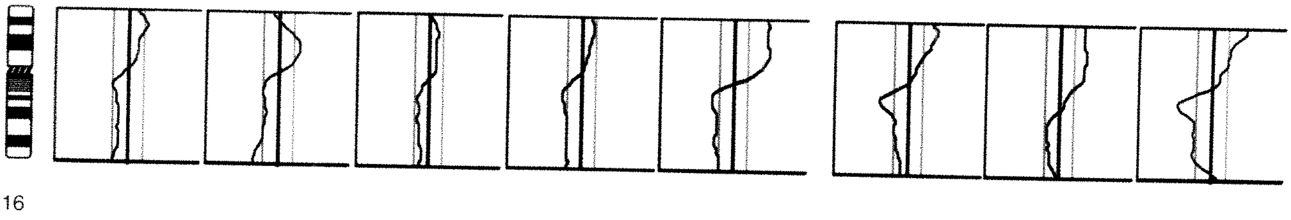
A number of known genes are located in the regions where amplifications were detected by CGH, including *myc* (8q24), *erbB2* (17q11) and cyclin D1 (11q13), and for deletion *p53* (17p13) and E-cadherin (16q22). While the greater number of 17p deletions in the group with recurrent breast cancer was not significant, it was in keeping with published data suggesting that 17p deletion is associated with a poor prognosis[24].

Although the finding of a MRO at 8q23 (rather than at c-*myc*, 8q24) may have resulted from marginal misalignment of the captured chromosome image with the ideogram, or fluorescence flaring of a high-level amplification, it supports data from Isola *et al.*[10] and Hermsen *et al.*[22] that c-*myc* may not be the sole proto-oncogene on 8q amplified in breast cancer.

Chromosome 17 exhibited a complex pattern of CGH changes, with 21 of the cancers showing at least one abnormality. The high level of amplification of distal 17q21-25[21] still has no convincing candidate gene. Centromeric to this locus, amplification at 17q12 is likely to represent amplification of the *HER2* oncogene. *HER2* amplification is known to occur in 25 per cent of breast



a Tumour recurrence



b No recurrence

Fig. 2 Different patterns of genetic abnormalities characterize tumour groups. The blue line represents a green : red fluorescence ratio of 1·0 (no loss or gain), the green line represents the threshold for amplication and the red line represents the threshold for deletion. **a** In five of 20 tumours that recurred, loss of 17p13 was found in association with a peak of relatively high copy number at 17q21-22. **b** In the group with no recurrent breast cancer, eight of 20 tumours showed gain of 16p and loss of 16q. This combination was not seen in patients with recurrent cancer

cancers[4,25,26], correlating with relapse and survival rates, and usually involving more than ten copies of the gene. Such a high copy number was not reflected in the size of the amplification peak on the CGH profile, probably reflecting difficulties with the interpretative software when dealing with multiple copies of small-sized amplicons. The proximal 17q12 amplification was independent of the much broader telomeric 17q21-25 site, but was more commonly seen in CGH profiles with multiple changes and particularly with 17p13 (*p53*) loss (*Fig. 2a*). This suggests cooperation between *p53* and *HER2*, mediated by chromosomal amplification of centromeric 17q (classical gene amplification) and deletion of the entire short arm of chromosome 17 (allelic loss). Detailed examination of individual CGH profiles revealed five tumours with a specific 17q12 amplification peak and loss of 17p in the group with recurrent tumours (*Fig. 2a*), compared with none in the group with no recurrence ($P = 0.05$, Fisher's exact test). Although material was not available for tumour grading in the present series, *HER2* amplification appeared to be associated with grade 3 cancers using CGH[15], in keeping with data from other sources.

The abnormalities of chromosome 16 identified in half of the tumours examined also involved specific patterns of gain and loss (*Fig. 2b*). Chromosome 16 is particularly interesting to cytogeneticists because it is known to be associated with an unbalanced translocation between the long arms of chromosomes 1 and 16 [der(16)t(1;16)(q10;q10)]. This derived chromosome is believed to occur as a consequence of crossover between the homologous repeat sequences of the pericentromeric regions of the long arms of chromosomes 1 and 16, an unbalanced rearrangement that is always associated with loss of 16q and gain of 1q and 16p. While the findings in a significant proportion of all breast cancers are consistent with a der1;16 translocation, others show different CGH abnormalities of chromosomes 1 and 16, suggesting that it is not locus-specific translocation (gene disruption) *per se* but DNA copy number change that is important. In this respect the der16 chromosome may represent a mechanism for selecting gain-of-function mutations on chromosomes 1q and 16p, and loss-of-function mutations on chromosome 16q, in one cytogenetic process. While no particularly strong candidate genes have yet been identified on 1q and 16p, the E-cadherin gene (16q22) is likely to be the target knocked out on chromosome 16q.

As well as a biological role in tumorigenesis, Roylance *et al.*[15] have suggested that the specific pattern of chromosome 16 abnormalities provides evidence that grade 1 tumours do not evolve into grade 3 tumours, which are associated with poor prognosis. The present data provide collateral evidence: eight of 20 tumours from women with no recurrent disease after 7 years had gain of 16p and loss of 16q (usually associated with gain of 1q), whereas none of 20 in the group with recurrent breast cancer had the same abnormalities (*Fig. 2b*) ($P = 0.002$, Fisher's exact test). These data support the hypothesis that alternative genetic pathways in the evolution of breast cancer are associated with different clinical outcomes[15,16,27]. Furthermore, 16p gain and 16q loss was seen more often in profiles with relatively few changes, or indeed with this single change, suggesting that this may represent an early genetic event in a subset of patients with primary breast cancer with a relatively good prognosis. Most previous studies have focused on loss of 16q, but overall gain of 16p was more common (and occurred in five further cancers). The importance of 16p has not been highlighted previously and merits further investigation.

With a destabilized karyotype (through aneuploidy) central to chromosomal aberrations early in tumorigenesis[28], subsequent amplifications and deletions may be responsible for determining a patient's outcome. Using cancer DNA from patients with breast cancer followed in the medium term, it can be proposed that 16p amplifications (gene(s) unknown) and 16q deletions (of E-cadherin) are together associated with a good prognosis, whereas 17p deletion (*p53*) and 17q amplification (*HER2*) co-segregate in a group of cancers and are associated with poorer prognosis. Furthermore, 16q loss and 17q21 gain are associated with morphological subtypes of breast cancer[29] and with prognostic indicators[19]. The use of CGH data provides supportive evidence that karyotypic studies of chromosomal abnormalities can enhance the understanding of the biology of breast cancer and indicate a molecular pathology associated with disease behaviour. Testing of this hypothesis will require a larger series of patients with breast cancer in order to examine the associations identified in this pilot study and their clinical significance.

Acknowledgements

The authors thank Tenovus (Scotland) and Breast Cancer Research Scotland for financial support for the CGH studies, and the patients and staff of Ninewells Hospital Breast Unit for their support.

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Original article

Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism

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Background: The purpose of this study was to evaluate the long-term efficacy of adrenalectomy on blood pressure control in patients with primary hyperaldosteronism (HA), and to analyse the cost of adrenalectomy compared with non-surgical management of HA over the patient's lifetime.

Methods: All patients who underwent an adrenalectomy for HA were recalled to the endocrine surgical clinic. Data gathered included blood pressure, aldosterone : renin ratios and medication. Total costs for adrenalectomy and ongoing medications were compared with the estimated costs of lifelong medical therapy alone.

Results: Twenty-four adrenalectomies were performed for HA, with one death. The mean follow-up was 42 (range 13–97) months. Long term, there was a significant decrease in both the mean diastolic and systolic blood pressure. The aldosterone : renin ratio decreased in 21 patients. Of these patients, 20 were either off all antihypertensives (eight) or had a reduction in medication (12). An increased aldosterone : renin ratio occurred in two patients, both of whom required an increase in antihypertensive medication. Using the predicted life expectancy, the mean estimated cost savings over the lifetime of each patient undergoing adrenalectomy compared with medication alone was Canadian $31 132.

Conclusion: Adrenalectomy for HA resulted in significant long-term reduction in blood pressure. Adrenalectomy for HA is a significantly less expensive than long-term medical therapy alone.

Presented to the Royal Australasian College of Surgeons, Adelaide, South Australia, Australia, May 2002

Paper accepted 11 July 2002

British Journal of Surgery 2002, 89, 1587–1593

Introduction

Primary hyperaldosteronism (HA) is a relatively rare cause of hypertension resulting from the overproduction of aldosterone. Primary hyperaldosteronism has generated a great deal of interest among surgeons since Jerome Conn first described the excision of a 4-cm adrenal cortical adenoma in 1955[1]. Conn predicted that a high percentage of hypertensive patients would be found to have adrenal cortical tumours producing aldosterone as a cause of their hypertension. However, this has been demonstrated to be an overly optimistic prediction, with the incidence of HA among the hypertensive population traditionally quoted in the range 0·05–2 per cent[2,3]. More recently, however, studies from a number of centres have indicated that the prevalence of HA in the hypertensive population is much higher than previously thought, with rates ranging from 5 to 16 per cent[4–8]. This increased recognition of HA has been attributed to the more frequent use of plasma aldosterone : renin ratios as a screening test for HA in the hypertensive population[9].

The classification of HA presently includes: a solitary aldosterone-producing adenoma (APA), accounting for about 65–75 per cent of cases including angiotensin II-sensitive, angiotensin II-resistant tumours and solitary or multinodular adenomas, against a background of adrenal cortical hyperplasia (recently termed primary adrenal hyperplasia (PAH) by Irony[10]); idiopathic hyperplasia of the adrenal gland (IHA), accounting for 25–30 per cent of cases; and unilateral hyperplasia, occurring in approximately 1–2 per cent of patients. Other rare causes of HA include glucocorticoid-remediable hyperaldosteronism and adrenal cortical carcinoma[10–14].

It is generally accepted that adrenalectomy is the treatment of choice for management of APA and that IHA is best treated medically[2, 3,15,16]. However, with the advent of improved medical therapies for hypertension some groups have demonstrated that patients with unilateral APA can be managed adequately in the long term using medical therapy alone[17–20].

Recently, increased emphasis has been placed on economic factors in healthcare decision-making. Increasingly, the physician is called on to consider the financial ramifications of various treatment options. In view of the increased frequency with which HA is being diagnosed and the suggestion that APAs can be treated with medical therapy alone, it was relevant to examine whether surgery offers a financial advantage over medical therapy in the long-term treatment of HA.

The purpose of this study was to analyse both the long-term efficacy of adrenalectomy in patients with HA and to compare the estimated costs associated with adrenalectomy with those of non-surgical management of these patients over their estimated lifetime.

Patients and methods

Using the surgical database of the senior author, the charts of all patients who underwent adrenalectomy over the past 9 years were reviewed. All patients who underwent adrenalectomy for HA were identified. These patients were contacted and recalled to the endocrine surgical clinic for review. Data gathered included all pertinent preoperative information such as blood pressure obtained from the preoperative assessment clinic before surgery, all antihypertensive medication, preoperative aldosterone : renin ratios, and localization studies (computed tomography (CT), selective venous sampling (SVS), postural testing and NP-59 nuclear medicine scans). The type of surgical procedure and length of stay in hospital were documented. At follow-up clinic, current medication and two readings of the patient's supine blood pressure measured 5 min apart were obtained. This allowed the patient time to settle into the clinic environment. The lowest blood pressure was recorded and used for analysis. Serum aldosterone and renin levels were measured. A subjective assessment of the patient's perception of blood pressure control was obtained by asking the patient to comment on whether his or her blood pressure control was improved, unchanged or worse than it was before surgery.

The estimated cost of treating HA with adrenalectomy was the total hospital admission cost plus the cost of any ongoing antihypertensive medication for the patient's estimated lifetime. The cost of treating HA using medical therapy alone was estimated by extrapolating the cost of medication taken before surgery for the duration of the patient's life.

The total cost of hospital admission for the adrenalectomy procedure was obtained from the Corporate Data Department of the Calgary Health Region. The total cost included all the direct and indirect costs associated with the admission for adrenalectomy, including medical staff payments. The cost of purchasing each antihypertensive medication was obtained from the Foothills Hospital outpatient pharmacy. The drug costs were based on the cost to an individual of purchasing the medication in the community setting in April 2001. Calculations were based on a life expectancy in the Calgary region of 76·7 years for men and 81·6 years for women[21]. Similarly the cost of any antihypertensive medication that was continued following adrenalectomy was estimated, based on medication prescribed at final follow-up. All costs were adjusted for inflation and expressed in Canadian dollars. Utilizing standard health economic evaluations, all anticipated costs were discounted at an annual rate of 3 per cent[22]. Comparisons were then performed between the costs of surgical treatment of HA and the estimated lifetime costs of continuing medical therapy alone. The overall cost saving between the two groups was calculated by subtracting the cost of surgical treatment and medication from the estimated cost of medical therapy alone for each patient. These costs were expressed as means with 95 per cent confidence intervals, and descriptive statistics were used to analyse any differences[23].

The alpha for statistical significance was set at $P < 0{\cdot}05$. Comparison of the preoperative and postoperative aldosterone : renin ratios was made using the Wilcoxon signed rank test. The paired *t* test was used to compare differences in blood pressure measurements, plasma aldosterone levels, renin activity and costs of therapy. Statistical analysis was performed using the Stata® software package (Stata® Corporation, College Station, Texas, USA).

Results

Between January 1992 and September 2001, 93 adrenalectomies were performed in 86 patients by the senior author. Of these patients, 24 (28 per cent) underwent unilateral adrenalectomy for HA. No perioperative morbidity was reported in 23 of the patients. There was one postoperative death from a pulmonary embolus. This death represented a postoperative mortality rate of 4 per cent for the patients with HA and 1 per cent for all patients undergoing adrenalectomy for any indication during the 9 years. The remaining 23 patients were all contacted and asked to return to the clinic. The mean follow-up was 42 (range 13–97) months. Twenty-one patients returned to the clinic for evaluation. Two patients, who were unable to travel to Calgary for this study, were assessed by the family physician and the relevant information was forwarded. Patient demographics, blood pressure recordings and biochemical measurements are summarized in *Table 1*.

The diagnosis of HA was made in all of these hypertensive patients by demonstrating spontaneous hypokalaemia (n = 18), raised aldosterone : renin ratios greater than 2500 pmol/l per mg/l/s (n = 23) and raised urinary aldosterone levels (n = 1). All but two of the patients had an adrenal abnormality identified by CT. Further lateralization studies were done in 20 patients. SVS was attempted in 17 patients and was successful in lateralizing the tumour in 16. Postural testing was done in two patients, only one of whom demonstrated evidence of APA, and NP-59 scan demonstrated concordant imaging in one patient. The remaining four patients had no further lateralization studies beyond CT. Twenty-three patients were believed to have HA secondary to a unilateral adenoma. One patient was known to have bilateral adrenal hyperplasia (IHA) and became refractory to extensive medical therapy. SVS demonstrated a significant gradient of aldosterone production from the left adrenal gland, and this gland was subsequently removed.

Table 1 Patient characteristics

No. of patients	24
Age (years)	52
Sex ratio (M : F)	20 : 4
Mean follow-up (months)	42 (31, 53)
Aldosterone : renin ratio (pmol/l per mg/l/s)	
Preoperative	19 970 (11 796, 28 140)
Postoperative	3 486 (580, 6 392)*
Systolic blood pressure (mmHg)	
Preoperative	164 (153, 176)
Postoperative	134 (129, 140)†
Mean decrease	29 (19, 39)
Diastolic blood pressure (mmHg)	
Preoperative	98 (90, 106)
Postoperative	85 (81, 89)†
Mean decrease	13 (6, 20)

Values are mean (95 per cent confidence interval). *P < 0·001 *versus* preoperative (Wilcoxon signed rank test); †P < 0·001 *versus* preoperative (paired t test)

The majority of procedures (19) were performed laparoscopically. In three patients the operation was converted to an open procedure for technical reasons and two patients had a posterior approach (*Table 2*). The laparoscopic procedure was associated with a shorter hospital admission, but there was no significant difference between the mean total cost of admission for the open *versus* laparoscopic adenalectomy (P = 0·25).

Histopathological examination of the resected adrenal glands showed that 13 were solitary adrenocortical adenomas (APAs) with a mean diameter of 2·1 cm. In eight patients a cortical nodule was found in a background of hyperplasia (PAH); the mean diameter of nodule was 1·9 cm. Three patients had hyperplasia (*Table 3*.)

The supine systolic and diastolic blood pressure recordings before operation, at 6 months after operation and at long-term follow-up are shown in *Fig. 1*. There were significant decreases in both systolic and diastolic blood pressure at the 6-month interval compared with preoperative values (P < 0·001). This decrease was maintained at long-term follow-up (P < 0·001).

No patient required potassium supplements after operation. Eight patients no longer required any antihypertensive medication and a further 12 were prescribed reduced doses or a reduced number of antihypertensive medicines at final follow-up. Two patients had an increase in antihypertensive medication and one had no change in his antihypertensive regimen at long-term follow-up (*Table 4*). When asked whether their blood pressure control was better, worse or unchanged following the adrenalectomy, 21 patients said that it was better controlled.

Table 3 Histopathology of the adrenal glands

Histopathology	No.
Solitary adrenocortical adenoma (APA)	13
Primary adrenocortical hyperplasia	8
Hyperplasia (IHA)	3*

*One patient with known bilateral hyperplasia before operation. APA, aldosterone-producing adenoma; IHA, idiopathic hyperplasia of the adrenal gland

Table 2 Operative procedure and length of hospital stay

	No. of patients	Length of stay (days)	Mean total cost (Canadian $)
Laparoscopic adrenalectomy	19	3·6	7 941 (5 891, 9 991)
Open adrenalectomy	5	6·6	10 444 (5 643, 15 245)*

Values in parentheses are 95 per cent confidence intervals. *P = 0·25 *versus* laparoscopic (paired t test)

The mean preoperative aldosterone : renin ratio was 19 970 pmol/l per mg/l/s. This ratio was significantly reduced at final follow-up ($P < 0{\cdot}001$) compared with the preoperative value. There were five patients in whom the aldosterone : renin ratio failed to decrease below 2500 pmol/l per mg/l/s after operation. One patient was known to have bilateral adrenal hyperplasia before operation and normalization of the aldosterone : renin ratio was not therefore expected. Two of the five patients had an increased aldosterone : renin ratio, both of whom had an increase in blood pressure at follow-up. Both of these patients in whom surgery failed had a normal CT scan, SVS lateralizing to one side, and were found to have adrenal hyperplasia in the removed adrenal gland. The remaining two patients both had a significant decrease in aldosterone : renin ratio compared with the preoperative value. Both required less medication after operation but not complete withdrawal. The mean preoperative and postoperative aldosterone : renin ratios according to the histological type and blood pressure control are summarized in *Table 5*. There was a significant difference in preoperative aldosterone : renin ratio between patients with a solitary APA and those who had adenoma/nodule in a background of hyperplasia ($P = 0{\cdot}02$), with the former having a higher preoperative ratio. There was no difference in postoperative aldosterone : renin ratio between these two groups ($P = 0{\cdot}1$). Although patients who had ceased all medication at long-term follow-up appeared to have a lower aldosterone : renin ratio than those who had either a decrease or increase in the amount of antihypertensive medication, these differences were not statistically significant ($P = 0{\cdot}26$ and $P = 0{\cdot}11$ respectively).

Table 4 Change in antihypertensive medication following surgery and subjective measure of blood pressure control

	No. of patients
Medication after operation	
None	8
Decreased*	12
No change	1
Increased†	2
Subjective blood pressure control	
Improved	21
No change	1
Worse	1

*Decrease in dosage or in number of antihypertensives required at long-term follow-up; †increase in antihypertensive medication requirement at long-term follow-up compared with before operation

The cost of surgery and estimated costs of medical therapy alone are shown in *Table 6*. The total costs of surgical admission plus the additional costs of continuing any antihypertensive therapy, as determined by medication taken at the last follow-up, were compared with the

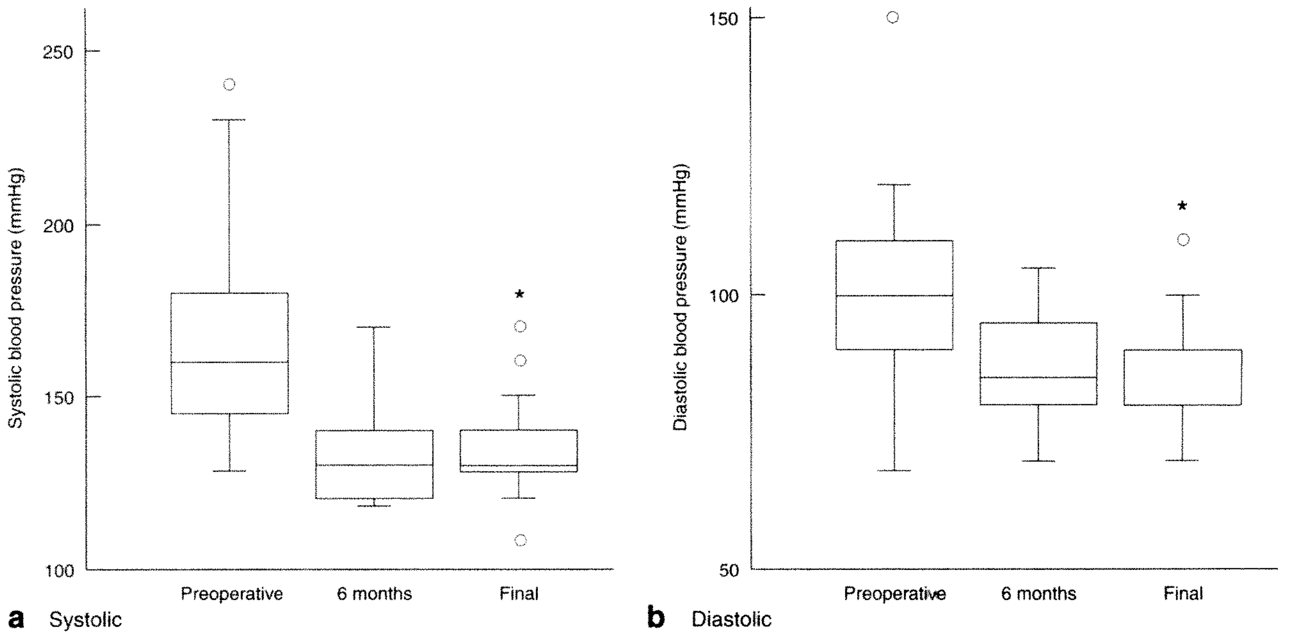

Fig. 1 **a** Systolic and **b** diastolic blood pressure measurements before operation, 6 months after operation and at final follow-up. Median and interquartile range are indicated by horizontal bars and boxes, respectively. *$P < 0{\cdot}001$ *versus* preoperative (paired t test)

Table 5 Mean aldosterone : renin ratios

		Mean aldosterone : renin ratio (pmol/l per mg/l/s)	
	No. of patients	Before operation	After operation
Pathology of gland			
APA	13	27 000	529
PAH	8	9 545¶	3 073
IHA	3	17 291	16 417
Postoperative medication			
None*	8	33 650	562
Decreased†	12	14 367	2 909
No change/increase‡	3	5 875	13 592

APA, aldosterone-producing adenoma; PAH, primary adrenal hyperplasia, adenoma in a background of hyperplasia; IHA, hyperplasia of the adrenal gland without nodules. *Normotensive on no medication; †normotensive on decreased number and/or dose of antihypertensives; ‡no change or increase in number or dose of antihypertensives at long-term follow-up. ¶P = 0·02 *versus* APA (paired t test)

Table 6 Estimated costs of medical and surgical therapy

	Cost (Canadian $)*
Adrenalectomy	8 463 (6 680, 10 246)
Adrenalectomy plus ongoing antihypertensive medication	19 960 (4 361, 116 839)†
Estimated cost of medical therapy alone	39 080 (27 493, 50 667)
Estimated cost savings for adrenalectomy per patient	31 132 (– 7 886, 100 265)

Values are mean (95 per cent confidence interval). *All costs adjusted for inflation. †P = 0·014 *versus* medical treatment alone (paired t test)

estimated costs of continuing medical therapy alone. Adrenalectomy, including any ongoing medication for HA, was significantly less expensive than the estimated cost of medical therapy alone (P = 0·014). The overall cost for the adrenalectomy group included costs incurred by the patient who died after operation. The mean estimated cost savings for adrenalectomy in HA over a patient's lifetime was $31 132 per patient.

Discussion

There has recently been increased debate in the literature on the true prevalence of HA[13,24,25]. Several authors have reported a rise in the prevalence of HA, estimated at between 5 and 16 per cent in the hypertensive population[4–8,13]. These higher rates are probably a result of the increased use of non-invasive screening and diagnostic tests such as CT and aldosterone : renin ratios. Although some caution has been expressed about the use of aldosterone : renin ratios in all patients, most authorities would agree that in patients with clinical suspicion of HA, the aldosterone : renin ratio is a good screening tool[8,9,24]. From a review of historical data from this institution, an aldosterone : renin ratio greater than 2500 pmol/l per mg/l/s was considered suspicious for HA and a value greater than 4000 pmol/l per mg/l/s was considered diagnostic. Although there was a significant drop in the aldosterone : renin ratio after operation in all patients whose blood pressure improved, there was no difference in the absolute aldosterone : renin ratio between patients who were cured and those who had a decrease in antihypertensive requirements. In this study surgery failed in the only two patients who demonstrated a rise in aldosterone : renin ratio at final follow-up. Although the number of patients is small, it would appear that a fall in aldosterone : renin ratio reflects surgical success.

Cure rates for HA following adrenalectomy have been reported to be as high as 77 per cent in the literature[11,26]. In this series, in which cure was defined as the patient being normotensive (less than 140/90 mmHg) and entirely free from all antihypertensive medication at final follow-up, the cure rate was only 35 per cent (eight of 23 patients). However, this figure is consistent with the findings of others who have reported cure in only 32–50 per cent of surgically treated patients using a similarly stringent definition of 'cure'[20,27–29]. It was found that younger patients, the response to spironolactone, a shorter duration of hypertension and higher preoperative aldosterone : renin ratios correlated with the resolution of hypertension[27,30]. In the present series a further 12 patients (52 per cent) were normotensive with a decrease in the number or dosage of antihypertensive medicines, giving a total of 87 per cent in whom adrenalectomy improved blood pressure control.

Recently the spectrum of surgically correctable unilateral disease causing HA has widened[10,12–14,31]. In this series eight patients had adenoma/nodules in a background of hyperplasia (PAH) and two patients appeared to have unilateral hyperplasia. All but one of these patients had preoperative functional lateralization on SVS or NP-59 scan. Seven of the patients with PAH had an improvement in blood pressure and one patient is off all medication. PAH is a form of autonomous aldosteronism that when proven to be unilateral in nature on functional assessment can be treated successfully with unilateral adrenalectomy[11,13,32]. Lo *et al.*[11] found PAH in 20 of the 46 adrenalectomy specimens in their retrospective series. Contrary to the present results, 70 per cent of their patients with PAH were normotensive following surgery, allowing them to conclude that PAH was not a risk factor for persistent hypertension following adrenalectomy.

Unilateral hyperplasia is a rare cause of HA that probably represents an intermediate state between APA and IHA. Until now, there have been no reported cases of recurrence following adrenalectomy in this condition[12]. In this series the operation failed in two patients in whom preoperative CT failed to demonstrate anatomical lesions, but who had lateralization to one adrenal gland on SVS. The pathological findings in the resected adrenal gland showed hyperplasia alone. Although initially both patients demonstrated an improvement in blood pressure control, at long-term follow-up both required additional antihypertensive medication and had an increase in aldosterone : renin ratio. Unlike the reported cases in the literature, these two patients with 'unilateral hyperplasia' at the time of surgery have now developed hyperaldosteronism from the contralateral gland, illustrating the need for long-term follow-up of these patients.

The cost of surgical management was compared with the estimated cost of treating the same patient with lifelong medical therapy alone by using a simple model that performed a cost minimization analysis of surgical therapy *versus* primary medical therapy. A cost minimization analysis is one of four forms of recognized economic evaluation in health care[22,33]. It is used to compare treatment modalities, that are considered to be similar in clinical outcome. The estimated cost of continuing the patients' preoperative antihypertensive throughout their expected lifetime was significantly greater than the cost of surgical management. Adrenalectomy was a cheaper form of treatment in the present patients primarily due to savings made on the long-term purchase of antihypertensive medications, made possible by the reduction in the patients' blood pressure after operation. As this study was performed in the setting of a fully publicly funded healthcare system, the cost savings represent savings from the perspective of the community and/or society, not just to the acute-care facility.

A potential weakness of the model used to estimate the cost of long-term medical therapy in HA is the fact that the calculations were based on the average life expectancy of individuals within the Calgary area. This may have overestimated the life expectancy in the study group. Although there was one death in the adrenalectomy group, it is not known whether the blood pressure in patients with APA treated non-surgically will become progressively more difficult to control over time and, for this reason, whether the life expectancy of patients with HA treated medically is equal to that of the general population. Ghose *et al.*[18] reported no death, stroke or cardiac events in any of the 24 patients with APA treated medically for at least 5 years. In an attempt to reflect the significance of the death in the present surgical group, this patient's surgical costs including intensive care unit admission were analysed with those of the remaining patients. For the purposes of the analysis, it was assumed arbitrarily that the patient's medication would have been unaltered by the adrenalectomy and that without surgery he would have a normal life expectancy. Even including the high perioperative costs involved with this one patient, the overall cost of adrenalectomy for the group as a whole was still cheaper than medical therapy alone.

Although this study attempted to measure opportunity cost by including the direct costs of adrenalectomy, the cost of the hospital admission and the long-term cost of ongoing medications, it was not possible to measure all of the opportunity costs associated with both treatments. Opportunity costs include not only the direct cost of treatment but also cost of treatments averted and the cost to patients such as time off work[34]. The potential loss of income for the patient was not factored into the overall cost in the adrenalectomy group. Nor could any additional cost associated with medical therapy, such as morbidity associated with the medication, changes in the type and amount of antihypertensives needed, and the number of primary care visits, be estimated and factored into the cost of non-surgical management because of the theoretical nature of the study.

Recognizing the limitations to this cost–benefit analysis, it would, however, appear that adrenalectomy for surgically amenable HA was significantly less expensive than long-term medical therapy alone. Adrenalectomy for HA resulted in significant long-term reduction in blood pressure. Normalization of the aldosterone : renin ratio appeared to correlate with surgical success.

Acknowledgements

M.S. is supported in part by the Mary-Jo Reeve Traveling Fellowship and the Division of Surgical Oncology at the University of Calgary.

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Original article

Nitric oxide enhances experimental wound healing in diabetes

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Background: Diabetes is characterized by a nitric oxide deficiency at the wound site. This study investigated whether exogenous nitric oxide supplementation with the nitric oxide donor molsidomine (*N*-ethoxycarbomyl-3-morpholinyl-sidnonimine) could reverse the impaired healing in diabetes.

Methods: Wound healing was studied by creating a dorsal skin incision with subcutaneous polyvinyl alcohol sponge implantation in diabetic and non-diabetic rats. Half of each group was treated with molsidomine. Collagen metabolism was assessed by wound breaking strength, hydroxyproline (OHP) content, RNA expression for collagen type I and III, and matrix metalloproteinase (MMP) 2 activity in wound sponges. Wound fluid, plasma and urinary nitric oxide metabolite levels, and the number of inflammatory cells were assessed.

Results: OHP content and wound breaking strength were significantly increased by molsidomine. MMP-2 activity in wound fluid was decreased in diabetes and upregulated by nitric oxide donors. The impaired inflammatory reaction in diabetes was unaffected by nitric oxide donor treatment and *ex vivo* nitric oxide synthesis was no different between wound macrophages from control and diabetic animals, suggesting that the nitric oxide deficiency in the wound is due to a smaller inflammatory reaction in diabetes.

Conclusion: The nitric oxide donor molsidomine can at least partially reverse impaired healing associated with diabetes.

Paper accepted 10 July 2002

British Journal of Surgery 2002, **89**, 1594–1601

Introduction

The problem of impaired healing in diabetes is still not understood. However, all stages of the complex wound healing cascade, including inflammation, proliferation, angiogenesis and matrix formation, are impaired. Decreased chemotaxis, phagocytosis, bacterial killing and antioxidant levels[1–3] during the early phase of repair have all been related to impaired healing in diabetes. Growth factor depletion[4,5], increased glucocorticoid levels[6], decreased cell proliferation[7,8] and upregulation of apoptosis[9] characterize the later phases of healing in diabetics, resulting in poorer granulation tissue formation. Decreased α-actin smooth muscle expression[9] and an excess of adipose tissue[10] may also affect healing in diabetes. Local administration of growth factors has been explored as a potential clinical treatment, but the results have been mostly disappointing. Restoration of blood glucose by insulin partially reverses some of the diabetes-induced wound healing deficiencies such as restoration of insulin-like growth factor levels, and improvement of bacterial killing and collagen metabolism[11,12]. Few therapeutic alternatives are therefore available to reverse impaired healing in diabetes.

The role of nitric oxide as a mediator in wound healing has been elucidated recently[13]. Administration of supplemental L-arginine, the sole substrate for inducible nitric oxide synthase (iNOS), improves wound healing[14], whereas lack of dietary L-arginine delays wound healing in experimental models[15]. Nitric oxide donors increase collagen synthesis in fibroblasts *in vitro* by an unknown mechanism[16] and accelerate wound closure when applied topically to excisional wounds[17]. Inhibition of iNOS impairs incisional and excisional healing[18,19]. Equivocal results have been obtained, however, from wound healing experiments in iNOS knockout mice[19,20]. Although nitric oxide regulates important functions of wound healing, such as cellular proliferation, angiogenesis, chemotaxis and epithelialization[21,22], the exact mechanism of action remains unclear.

Based on previous findings that diabetes is characterized by reduced nitric oxide levels in the wound environment[23], the present study investigated whether exogenous nitric oxide administration can restore the impaired wound healing in experimental diabetes, using molsidomine, a widely used antianginal drug which spontaneously releases nitric oxide.

Materials and methods

Materials

Molsidomine (*N*-ethoxycarbomyl-3-morpholinyl-sidnonimine) was purchased from Sigma (St Louis, Missouri, USA) and dissolved in ethanol/water (1/99 v/v).

Animals and induction of diabetes

The study was approved by the animal care committee. Male Sprague–Dawley rats (Harlan-Sprague Dawley, Indianapolis, Indiana, USA) were allowed to acclimatize for 1 week and were offered food and water *ad libitum* throughout the study. Nine days before wounding, 22 rats were injected intraperitoneally with streptozotocin (70 mg per kg body-weight in citrate buffer 0·1 mol/l, pH 4·5) to induce diabetes. Eighteen control rats were injected with citrate buffer only. Induction of diabetes (blood glucose greater 250 mg/dl) was confirmed by venous glucose measurement. Animals not achieving the diabetic state after 24 h were reinjected with streptozotocin and then excluded from the study if the glucose concentration was not greater than 250 mg/dl.

Half the control and half the diabetic group were treated with molsidomine (1 mg per kg body-weight per day), and the other half received ethanol/water (1/99 v/v) only. The treatment was administered by gavage three times daily in an approximate volume of 2 ml per gavage and started on the day of wounding. All animals were weighed daily and monitored for side-effects.

Wounding

Rats underwent a 7-cm dorsal skin incision and bilateral subcutaneous implantation of polyvinyl alcohol (PVA) sponges (M-PACT, Eudora, Kansas, USA) under intraperitoneal pentobarbital anaesthesia. The incision was closed with surgical staples. Ten days after wounding the rats were killed, blood was obtained by cardiac puncture and the following variables were analysed.

Blood chemistry

Blood glucose, protein, albumin, blood urea nitrogen and creatinine were measured in venous blood.

Urinary nitrate and nitrite

Four to five rats per group were kept in metabolic cages and urine was collected from postoperative day 3 to day 4. Samples were acidified to prevent bacterial overgrowth. Urine samples were analysed for nitrite and nitric oxide metabolite (NO_x) content as described below. Results are expressed as micromoles of NO_x per day per rat based on total volume of urine excreted.

Breaking strength

The dorsal skin pelt containing the incision was excised widely and cut by a multibladed guillotine into equal strips, each containing a segment of the healing scar. Immediately after death, four strips from each animal were analysed for wound breaking strength (WBS) using a constant-speed tensiometer.

Hydroxyproline content of sponges

The two most cephaled preweighed sponges were cleared of surrounding granulation tissue and used to measure hydroxyproline (OHP) content (micrograms per 100 mg sponge), an index of collagen deposition, as described previously[24].

Wound fluid analysis

Sponges were cleared of surrounding granulation tissue, and wound fluid was harvested and prepared for NO_x measurement as described previously[25]. Arginase activity was quantified spectrophotometrically by urea formation under optimal conditions and expressed as nmoles of urea per minute per milligram protein[26].

Extraction of wound cellular infiltrate

Four sponges per animal were use. The squeezed sponges were minced with iris scissors in complete Dulbecco's modified Eagle's medium (DMEM; Gibco Life technologies, Grand Island, New York, USA) containing glutamine, penicillin, streptomycin, fungizone and 1 per cent albumin. The cell suspension was passed through an 80 and 100 stainless steel mesh and combined with the cell pellet from the wound fluid preparation which was retrieved after the first spin (400g for 10 min). After lysis of red blood cells in ammonium chloride buffer, the cells were washed and counted using a Neubauer chamber. Viability was checked by trypan blue exclusion.

In vitro nitrite synthesis by wound macrophages

Wound cells ($1·5 \times 10^6$) were seeded into 24-well plates (Costar, Cambridge, Massachusetts, USA) in phenol red-free DMEM containing 1 per cent albumin and L-arginine 1 mmol/l, and cultured for 24 h. A macrophage-enriched wound cell population was obtained by vigorously washing off non-adherent cells 2 h after plating. Half of the macrophage-enriched wound cells thus obtained were stimulated with lipopolysaccharide 1 μg/ml and interferon-γ 10 units/ml (Boehringer Mannheim, Indianapolis, Indiana, USA). After 24 h the medium was harvested and the cells were lysed for DNA analysis by the Hoechst Dye technique as described previously[27]. Nitrite synthesis values were normalized for DNA concentration. Determination of nitrite was performed using the Griess reagent[28].

Northern blot analysis

One sponge per animal was used to extract RNA using TRIzol reagent (Gibco Life Technologies) following the manufacturer's instructions. Some 10–15 μg RNA was separated on 1·2 per cent agarose gels, transferred on to nylon membranes (Amersham Life Sciences, Arlington Heights, Illinois, USA) and cross-linked. After prehybridization using salmon sperm DNA, the blots were hybridized at 42°C using mouse collagen types I and III (gift from Dr Ksander, Celltrix, Palo Alto, California, USA) and rat glyceraldehyde-3-phosphate dehydrogenase (GAPDH) probes (generated by polymerase chain reaction). After washing, the blots were autoradiographed. Blots were reprobed with GAPDH to control for equal loading. Densitometry was performed using Image Quant™ software (Molecular Dynamics Image Quant™, Santa Barbara, California, USA). Results are expressed as the ratio of the density for collagen to that for GAPDH; controls were set at 1.

Zymography

The gelatinase activity of equal amounts of wound fluid proteins (*Table 1*) was measured following standard non-reducing sodium dodecyl sulfate–polyacrylamide gel electrophoresis on 7·5 per cent acrylamide gel containing 0·1 per cent gelatin type A as substrate (Fisher, Hampton, New Hampshire, USA), as described previously[29]. The gel was incubated overnight at 37°C in Tris-hydrochloride 50 mmol/l (pH 7·6), sodium chloride 0·2 mol/l, calcium chloride 5 mmol/l and 0·02 per cent (w/v) Brij35, stained in 0·25 per cent coomassie blue and destained.

Statistical analysis

Results are expressed as mean(s.e.m.). Statistical analysis was performed using analysis of variance with Fisher's post-hoc test. Significance was reached at $P < 0·05$. The data were analysed by Statview™ programme (Abacus Concepts, Berkeley, California, USA).

Results

Four of the 22 streptozotocin-injected rats did not become diabetic and were excluded. Two other diabetic animals were excluded because gastric gavage was not consistently possible. At the end of the study 18 control and 16 diabetic rats could be evaluated.

Treatment with molsidomine was well tolerated as demonstrated by the equal weight gain in the non-diabetic groups. Treatment with molsidomine resulted in significantly less weight loss in the diabetic rats (− 4(12) g for molsidomine-treated diabetic rats *versus* −21(7) g for saline-treated diabetic rats; $P < 0·05$).

Blood glucose values were significantly increased in the diabetic rats, but were not affected by molsidomine treatment (*Table 1*). Wound fluid protein levels, a reflection of the degree of the inflammatory response, were significantly lower in diabetic rats. BUN was also higher in the diabetic animals, most probably indicative of the increased protein catabolism. Molsidomine had no effect on any of these variables.

Molsidomine treatment significantly increased the fresh WBS in the diabetic group but did not affect WBS in the control group. This was paralleled by a significant increase in OHP content with molsidomine in the subcutaneously

Table 1 Blood chemistry and wound fluid protein levels

	Control + saline	Control + molsidomine	Diabetic + saline	Diabetic + molsidomine
Serum protein (g/l)	48·1(4·0)	49·3(4·3)	45·0(0·9)	46·1(1·2)
Glucose (mmol/l)	4·7(0·4)	4·3(0·2)	28·5(1·4)*	26·4(1·2)*
Blood urea nitrogen (mmol/l)	9·3(1·2)	8·1(0·3)	12·8(0·9)*	13·3(1·3)*
Wound fluid protein (g/l)	65·1(0·6)	68·8(1·1)	51·9(2·1)*	53·3(2·1)*

Values are mean(s.e.m.). *$P < 0·05$ *versus* control + saline (analysis of variance with Fisher's post-hoc test)

Table 2 Wound breaking strength and hydroxyproline content of polyvinyl alcohol sponges

	Control + saline	Control + molsidomine	Diabetic + saline	Diabetic + molsidomine
OHP content in PVA sponges (µg per 100 mg sponge)	1311(105)	1645(82)*	555(96)*	902(131)†
Wound breaking strength (g)	409(33)	417(25)	184(12)*	258(33)†

Values are mean(s.e.m.). OHP, hydroxyproline; PVA, polyvinyl alcohol. *$P < 0.05$ *versus* control + saline, †$P < 0.05$ *versus* diabetic + saline (analysis of variance with Fisher's post-hoc test)

implanted PVA sponges in both control and diabetic animals (*Table 2*).

Diabetic rats had significantly less NO_x in wound fluid than controls indicating a nitric oxide-deficient state (*Fig. 1*). Molsidomine treatment increased NO_x excretion in urine, but did not affect NO_x levels in wound fluid or plasma.

Zymograms of wound fluid, used as an indicator of gelatinase activity, showed significantly less activity in diabetes of an approximately 60-kDa protein, corresponding to MMP-2. Molsidomine treatment specifically increased this gelatinase activity in zymograms of control as well as diabetic rats (*Fig. 2*).

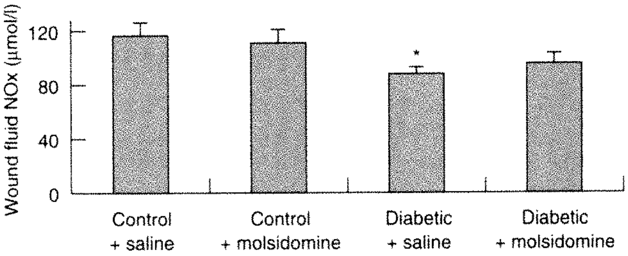
Northern blot analysis of collagen type I and III gene expression from the sponges showed a 25 per cent decrease in gene expression in the treatment groups compared with controls. *Fig. 3* shows one representative northern blot for collagen type I. For densitometry the northern blots were normalized against GAPDH and the non-treated groups were set at 1. Collagen type III gene expression was affected in the same way as collagen type I expression (data not shown).

The inflammatory response to wounding, represented by the number of cells isolated per sponge, was significantly decreased in diabetic rats compared with controls (approximately 40 per cent) but was unaffected by molsidomine treatment (*Table 3*). This was confirmed indirectly by a lower yield of RNA per sponge from the diabetic rats as well as a lower protein concentration in wound fluid. The *ex vivo* nitric oxide formation by wound-derived macrophages was approximately equal in all groups as was the increase in nitric oxide synthesis following exposure to lipopolysaccharide and interferon-γ (*Fig. 4*).

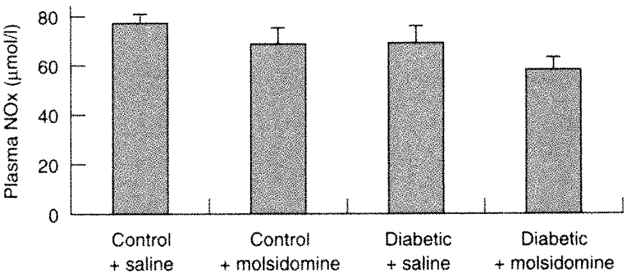
Arginase activity in wound fluid, representing the alternative pathway of arginine metabolism in wounds, was significantly lower in diabetic wound fluid (*Fig. 5*).

Discussion

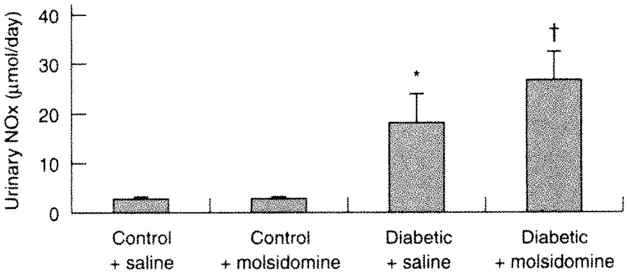
The present study confirms that diabetes is characterized by a nitric oxide-deficient state accompanied by decreased WBS, collagen deposition and a severely impaired inflammatory response. The nitric oxide donor molsidomine



a Wound fluid



b Plasma



c Urine

Fig. 1 Mean(s.e.m.) levels of nitric oxide metabolites (NO_x; nitrite and nitrate) in wound fluid (**a**), plasma (**b**) and urine (**c**). Wound fluid NO_x were significantly reduced in diabetic rats compared with controls. Molsidomine treatment did not significantly increase NO_x in either wound fluid or plasma. Urinary NO_x production was, however, significantly increased in diabetes possibly reflecting activation of the nitric oxide system after induction of diabetes and injury. The volume of urine excreted increased significantly after the induction of diabetes. *$P < 0.05$ *versus* control + saline, †$P < 0.05$ *versus* control + molsidomine (analysis of variance with Fisher's post-hoc test)

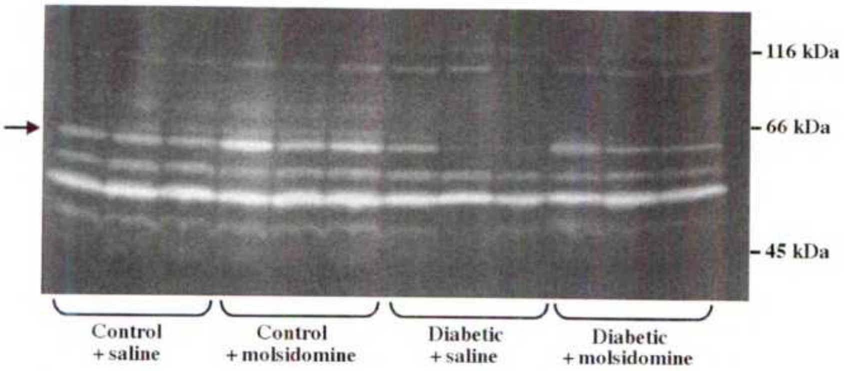


Fig. 2 Zymogram of three wound fluid samples from each group. Equal amounts of protein were loaded on to non-reducing sodium dodecyl sulfate–polyacrylamide gels and analysed as described above. Matrix metalloproteinase (MMP) 2 is an approximately 60-kDa protein (arrow). Diabetic wound fluids had lower MMP-2 activity than controls. Molsidomine increased MMP-2 activity in control and diabetic animals

Table 3 Inflammatory response measured as the number of infiltrating cells per sponge and cell viability

	Control + saline	Control + molsidomine	Diabetic + saline	Diabetic + molsidomine
Total cells per sponge (× 10^6)	4·19(0·39)	4·41(0·42)	2·41(0·45)*	2·93(0·39)*
Viability (%)	54·8(2·3)	53·5(3·4)	54·2(2·6)	50·4(2·6)

Values are mean(s.e.m.). $^*P < 0·05$ *versus* control + saline (analysis of variance with Fisher's post-hoc test)

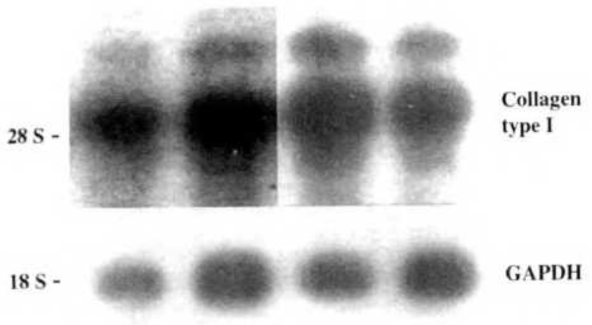
represents a potential treatment for acutely impaired healing in diabetes because it increased wound breaking strength by increasing the OHP content of the PVA sponges, a marker of collagen deposition. This nitric oxide donor did not affect collagen gene transcription[16] so a post-transcriptional regulatory mechanism has to be assumed.

The data further show that hyperglycaemia impairs the inflammatory response during wound healing as demonstrated by the decreased number of wound inflammatory cells in diabetes. Hyperglycaemia and nitric oxide are both known to impair the chemotactic response, but in this study cellular infiltration was unaffected by nitric oxide donor treatment (*Table 3*). The reduced inflammatory response involves reduced macrophage infiltration, a process essential for wound healing[30]. As the *in vitro* nitric oxide synthesis of wound-derived macrophages was no different between control and diabetic rats, the difference in accumulation of nitric oxide metabolites in wound fluid was rather due to the significantly smaller number of infiltrating cells. There was also no difference in nitric oxide production after *in vitro* stimulation of wound-derived macrophages with the cytokine mix. This suggests that inflammatory cells in the wound milieu are similarly sensitive to nitric oxide stimulation, although it is not certain that the *ex vivo* culture of macrophages fully reflects *in vivo* regulation. iNOS synthesis in both control and diabetic macrophages was not fully stimulated indicating that the level of nitric oxide stimulation during wound healing is tightly controlled physiologically.

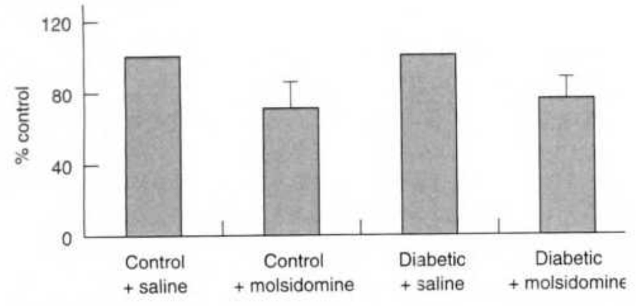
Nitric oxide donor treatment does not completely restore nitric oxide levels in wound fluid or plasma (*Fig. 1*). The effect of nitric oxide donor administration may be dependent on a threshold rather than a dose. So far, no study has demonstrated a correlation between levels of nitric oxide in wounds and outcome. This corresponds with a previously published study in which administration of nitric oxide donors to fibroblasts induced a significant increase in collagen synthesis within a small range[16] or with the long-lasting effect of a single transfection of iNOS complementary DNA in iNOS knockout mice[25]. It is conceivable that diabetic wounds are more susceptible to nitric oxide donor treatment since the wound is deficient in nitric oxide. The effect in non-diabetic rats might have been more pronounced if a higher dose of molsidomine was used. The dose chosen was rather low to avoid interference by the vasodilator effect of the nitric oxide donor. Molsidomine has an affinity for skin tissue[31] which might explain why it affects dermal wound healing with little systemic effect.

Interestingly there was significantly lower arginase activity in wound fluid from diabetic animals. Arginase is released into wound fluid by macrophage cell death[32].

However, fibroblasts also contribute to wound arginase activity[33]. The reduced arginase activity seems to be specific to the wound since liver arginase is upregulated in diabetes[34]. As arginase activity was unaffected by treatment with molsidomine it seems unlikely that this alternative pathway of nitric oxide metabolism is responsible for the effect in the treatment group.



a Northern blot



b Relative density

Fig. 3 **a** Representative Northern blot showing collagen type I gene expression. RNA was extracted from sponges and analysed for collagen type I expression using specific DNA probes. **b** For analysis, densitometric values in control groups were set at 1 and those in molsidomine-treated groups were given relative to this. Molsidomine treatment decreased collagen type I gene expression in both groups. The same effect was seen for collagen type III (data not shown). GAPDH, glyceraldehyde-3-phosphate dehydrogenase

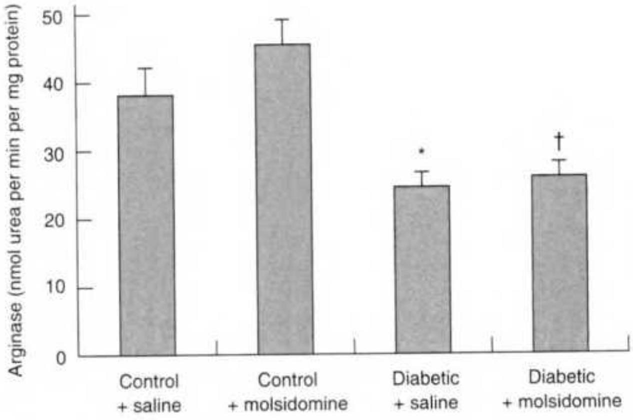


Fig. 5 Mean(s.e.m.) arginase activity in wound fluid. Arginase activity was significantly reduced in diabetic animals. The effect of impaired cellular infiltration in diabetic sponges was taken into account by expressing enzymatic activity with respect to protein content in wound fluid, so the reduced activity was due to a net reduction in activity. $^*P < 0.05$ *versus* control + saline, $†P < 0.05$ *versus* control + molsidomine (analysis of variance with Fisher's post-hoc test)

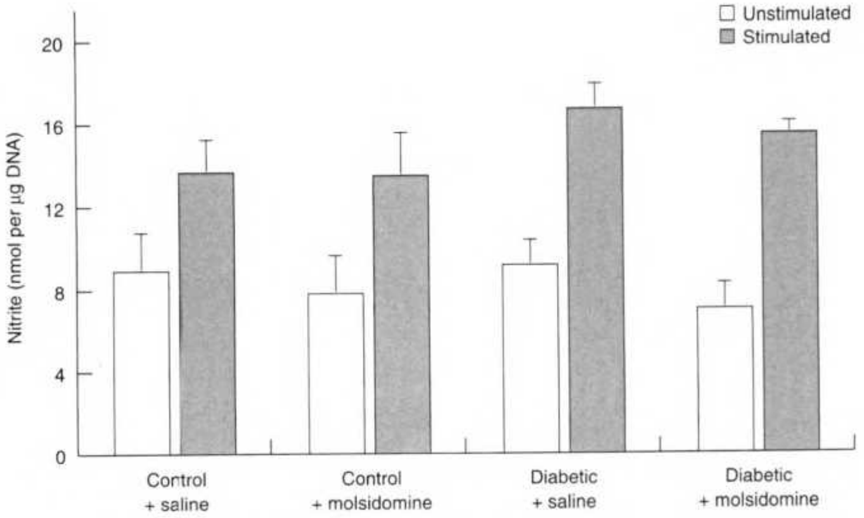


Fig. 4 Mean(s.e.m.) nitrite accumulation over 24 h in unstimulated wound macrophages or macrophages stimulated with cytomix (lipopolysaccharide–interferon-γ). Control and diabetic macrophages produced similar amounts of nitrite in culture. Stimulation with cytomix increased nitrite synthesis to the same extent in both groups

WBS, an indicator of the amount and quality of newly deposited collagen at the wound site, was significantly increased by nitric oxide donor treatment in diabetes. This effect was accompanied by increased OHP in the sponges indicating that the nitric oxide donor is probably acting by increasing new collagen formation. Northern blotting, however, revealed no effect of nitric oxide treatment on collagen gene expression. The wound fluid of diabetic animals had significantly less MMP-2 activity than controls, which was significantly increased by nitric oxide donor treatment (*Fig. 2*). MMP-2 originates primarily from fibroblasts and is involved in remodelling of wound healing[35]. Upregulation of MMP-2 might reflect increased matrix remodelling by molsidomine treatment.

It has been shown previously that arginine treatment also improves impaired healing in diabetes[36]. That molsidomine treatment modifies cytokine expression during wound healing and therefore improves collagen synthesis and breaking strength cannot be excluded.

In summary, administration of molsidomine can partially restore the impaired healing in diabetes by enhancing collagen synthesis and WBS. This may have therapeutic potential and needs further clinical evaluation.

Acknowledgements

Supported by grants from the Deutsche Forschungsgemeinschaft (Wi 1499/1-1) (M.B.W.) and no. GM54566 from the National Institutes of Health (A.B.).

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Original article

Low-cost laparoscopic cholecystectomy

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Background: Hospital managers are continually trying to decrease the cost of patient care. The aim of this prospective study was to propose changes that would decrease the operating room costs of laparoscopic cholecystectomy without affecting clinical results.

Methods: The study included 112 consecutive patients who underwent an elective cholecystectomy between January 1997 and December 2000. The procedure was changed in eight ways: the American position, open laparoscopy, reusable trocars, reusable instruments, bipolar coagulation of the cystic artery, intracorporeal ligature of the cystic duct, no use of suction lavage apparatus, and use of a surgical glove as a bag to extract the gallbladder. Complete compliance with the procedure, whether any abnormal operative events or complications occurred, the duration of hospitalization, and the material and labour costs of the procedure were recorded.

Results: There were no abnormal operative events. Only two patients suffered from postoperative complications. The mean duration of hospitalization was 55·8 h. Fifteen patients (13·4 per cent) were not hospitalized overnight. The operating costs fell from 560 euros before the study to 330 euros in 2000.

Conclusion: By applying simple measures, it is possible to decrease the operating room cost of laparoscopic cholecystectomy whilst maintaining good results. Such measures should be applied to other laparoscopic procedures.

Papers accepted 15 July 2002

British Journal of Surgery 2002, **89**, 1602–1607

Introduction

Many abdominal surgical procedures are now performed laparoscopically. Although this has proven to be of great value for patients and has decreased the overall cost of cholecystectomy[1,2], it has markedly increased operating theatre costs[3]. In Paris, for example, in the mid 1990s, the average operating theatre cost for a laparoscopic cholecystectomy was 762 euros, including 457 euros for materials and 305 euros for labour. These values are in keeping with those of other hospitals[4]. For the past two decades there have been strong incentives from hospital managers to decrease the cost of patient care; however, this may decrease the quality of the care delivered to patients. Therefore, the authors modified the laparoscopic cholecystectomy procedure in an attempt to decrease operating theatre costs. The aim of this study was to determine whether decreasing the costs would affect clinical results.

Patients and methods

Patients

The study included 112 patients who underwent elective laparoscopic cholecystectomy for symptomatic gallstones by one of the three senior surgeons (C.V., I.D. or D.F.) between January 1997 and December 2000.

One hundred and nineteen other patients who underwent an emergency procedure for acute cholecystitis in the same time period were excluded. Five patients in whom laparoscopic cholecystectomy was associated with laparoscopic treatment of common bile duct (CBD) stones were also excluded. Preoperative investigations included ultrasonography of the gallbladder, CBD and intrahepatic ducts, and measurement of blood levels of transaminases, alkaline phosphatase and γ-glutamyl transferase.

Twenty-one (18·8 per cent) of the 112 patients studied had signs predictive of CBD stones such as a history of acute pancreatitis or transient jaundice and/or an increase in one of the three biological markers and/or CBD diameter greater than 7 mm at ultrasonography. One week before cholecystectomy these patients underwent endoscopic ultrasonography, and immediate endoscopic sphincterotomy was performed in eight of them because CBD stones were discovered.

The main features of the 112 patients are shown in *Table 1*. There were more women than men. Most of the patients were in good health with a low American Society of Anesthesiologists (ASA) score. The duration of the biliary symptoms that led to the diagnosis of gallstones was extremely variable. Eleven patients had suffered from acute biliary pancreatitis, which was severe in seven cases and mild in four. These patients underwent laparoscopic cholecystectomy after complete resolution of the acute episode of pancreatitis. Thirty-one patients (27·7 per cent) had chronic cholecystitis defined at operation as thickening of the gallbladder wall and/or adhesions around the gallbladder and/or inflammation of the Calot triangle; 81 patients (72·3 per cent) had a normal gallbladder with no adhesions or inflammation.

Anaesthesia and postoperative analgesia

All patients were operated on under general anaesthesia. Patients were given 100 mg hydroxyzine orally 1 h before operation. The patients were anaesthetized[5] with sufentanil 0·2–0·3 µg/kg and thiopentone 5 mg/kg. Intraoperative analgesia was maintained with boluses of sufentanil (5–10 µg). During the operation 50 mg ropivacaine mixed with saline was injected above the liver and on each side of the gallbladder below the liver. This was repeated at the end of the operation before exsufflation of the peritoneum[5]. When the patients were in the recovery room, boluses of morphine were given to achieve adequate pain relief according to a ten-point verbal scale.

Table 1 Characteristics of 112 patients undergoing elective laparoscopic cholecystectomy

Mean (range) age (years)	53 (22–88)
Sex ratio (F : M)	86 : 26
Delay between first symptoms and operation	12 days to 5 years
Arterial hypertension	28 (25·0)
Coronary heart disease	10 (8·9)
Diabetes	7 (6·2)
Chronic obstructive bronchitis	7 (6·2)
Anticoagulant treatment	13 (11·6)
Mean ASA classification	1·44

Values in parentheses are percentages unless otherwise stated. ASA, American Society of Anesthesiologists

Operative procedure

The operation was performed through four trocars: two 10-mm trocars at the umbilicus and in the left upper quadrant, and two 5-mm trocars near the xyphoid process and in the right iliac fossa. Five instruments were used: two graspers (5 mm), one hook monopolar electrode, one pair of bipolar coagulation forceps and one pair of scissors. The Calot triangle was opened, and the cystic duct and artery were identified, dissected free, closed and separated. The gallbladder was then separated from its liver bed and a bag was used to extract it through the umbilical incision. No drains were used. As patients with signs predictive of CBD stones had previously been treated by endoscopic sphincterotomy, intraoperative cholangiography was performed in only nine patients (8·0 per cent) in whom an unexpectedly enlarged CBD was observed during operation. No CBD stones were found in any of these patients, none of whom had a history of acute pancreatitis. The operating procedure was changed in eight ways to decrease the cost of consumables during operation: (1) use of the American position, (2) open laparoscopy, (3) reusable trocars, (4) reusable instruments, (5) bipolar coagulation of cystic artery, (6) single intracorporeal ligature of cystic duct with resorbable suture (3/0 polyglactin (Vicryl®; Ethicon, Issy les Moulineaux, France), (7) non-use of a suction lavage apparatus, and (8) use of a surgical powder-free glove (Nutex®; Ansell Medical, Munich, Germany) as a bag to extract the gallbladder[6]. The possible decreased costs associated with these measures are indicated in *Table 2*. There were four surgical workers in the operating theatre: a senior surgeon, an assistant, a scrub nurse and a circulating nurse.

Costs

Only variable costs were studied. For every cholecystectomy, the costs of materials and labour were recorded. The cost of the materials was the sum of the costs of the consumables (mainly ligatures, sutures, gowns, drapes, sponges and antiseptic agents) and of maintaining reusable trocars and instruments, including cleaning, sterilization, packaging and repairs. This was calculated on a 4-year basis (1997–2000) by dividing the total maintenance cost of laparoscopic trocars and instruments by the number of laparoscopies performed for cholecystectomy during the same interval. This maintenance cost was 14·8 euros per procedure. The cost of labour was obtained by adding the costs of wages per unit of time to the number of individuals

Table 2 Possible savings resulting from adjustments designed to decrease the cost of elective cholecystectomy

Modification	Avoidance	Approximate saving (euros)
American position	Sterile boots	0·38
Open laparoscopy	Disposable Veress needle	17·73
Reusable trocars	Disposable trocars	179·26
Reusable instruments	Disposable instruments	272·73
Bipolar coagulation of cystic artery	Clips	39·70
Intracorporeal ligature of cystic duct with resorbable peritoneal suture	Clips	40·11
No lavage	Disposable cannula and catheter	22·98
Powder-free glove	Disposable commercial bag	37·27
Total		610·16

present during the procedure, multiplied by the length of the operation. All of these data were fed into the computer in real time by use of a program that has been specially designed for operating theatre management (Logibloc®; Varimed, Louveciennes, France). Fixed costs that are independent of the procedure, such as fluids, electricity and the costs of the anaesthesia, were not taken into account. The cost of cholecystectomy during the study period was compared to that of 50 cholecystectomies performed by the same surgeons in the year 1994–1995, before the changes were implemented.

Quality assessment

The quality of care was assessed by determining whether there was complete compliance with the procedure and whether any abnormal operative events or complications occurred during the 6-month follow-up period or during hospitalization.

Statistical analysis

Means were compared with Fisher's and Yates' statistical tables. $P < 0{\cdot}05$ was considered to be significant.

Results

Procedure (*Table 3*)

The eight changes used to try to decrease operative costs were applied in 77 (68·8 per cent) of 112 cholecystectomies during the study period (from three of 15 in 1997 to all 38 cholecystectomies performed in 2000). The low rate of complete compliance in the first 2 years was related mainly to two measures. First, with regard to the use of a disposable Veress needle to induce pneumoperitoneum, this practice was used in eight of 15 operations performed in 1997 and none of the 38 procedures carried out in 2000. Second, the practice of using a commercial bag to extract the gallbladder through the umbilicus was employed in four of 15 operations in 1997 and in no operation in 2000. The other changes were strictly applied for all patients from the beginning of the study.

Table 3 Changes in the use of open laparoscopy and of a surgical glove to extract the gallbladder during the study

Technique	1997 (*n* = 15)	1998 (*n* = 29)	1999 (*n* = 30)	2000 (*n* = 38)
Open laparoscopy	7	20	26	38
Disposable Veress needle	8	9	4	0
Glove	11	29	30	38
Disposable bag	4	0	0	0

The mean operating time was 106·8 min (104·8 min in 1997, 114·3 min in 1998, 105·4 min in 1999 and 102·0 min in 2000). During the control period the mean operating time was 103·6 min. In patients with intraoperative evidence of chronic cholecystitis, the mean operating time was significantly longer than in those with a normal gallbladder (127·0 *versus* 98·6 min; $P < 0{\cdot}05$).

Adverse intraoperative events

There were no conversions to laparotomy, no deaths during operation, no blood transfusions, no allergies to the glove used to remove the gallbladder, no loss of stone, and no other major complications. None of the operations required suction. The umbilical incision was contaminated with bile during extraction of the gallbladder in seven cases (6·2 per cent). It was never necessary to switch between reusable trocars or instruments and disposable ones during operation.

Postoperative complications

Postoperative complications occurred in two patients (1·8 per cent). An umbilical abscess was found 7 days after

Table 4 Changes in the total length of hospitalization of patients undergoing elective laparoscopic cholecystectomy from 1997 to 2000

Length of hospital stay	1997 (n = 15)	1998 (n = 29)	1999 (n = 30)	2000 (n = 38)
Mean (h)	64	51	58	51
≥ 3 days	6	7	4	5
< 3 days	8	20	25	22
Day cases	1	2	1	11

Table 5 Changes in the operating room costs of laparoscopic cholecystectomy before and after technical changes

	Cost (euros)					
	Before changes	After changes				
	1995–1996	1997	1998	1999	2000	Mean
Materials	348	142	75	65	59	85
Labour	212	265	297	253	271	272
Total	560	407	372	318	330	357

operation in one patient and drained spontaneously. To the authors' knowledge, the trocar site was not contaminated with bile during operation in this patient. The other patient had bile peritonitis, which was diagnosed 3 days after operation. Laparoscopy revealed a bile leak from an accessory bile duct in the gallbladder bed, which had not been seen during the primary operation. Treatment consisted of stitching the accessory bile duct closed and peritoneal lavage. None of the patients had any bile leak from the cystic stump or bleeding from the cystic artery. During follow-up, no patient had late stenosis of the CBD.

Length of hospital stay (*Table 4*)

Most of the patients (75·0 per cent) were admitted to hospital on the morning of the intervention. The mean length of hospitalization was 55·8 h. Patients with no medical history, ASA grade 1 and no anticoagulant therapy were in hospital for significantly less time (40·2 h) than the other patients (74·2 h) ($P < 0{\cdot}05$). Fifteen patients (13·4 per cent) underwent day-case laparoscopic cholecystectomy. The proportion of day cases increased from one of 15 patients in 1997 to 11 of 38 in 2000 after a day-case surgery programme was launched in the hospital.

Cost of the procedure (*Table 5*)

The mean operating room cost for elective cholecystectomy was 357 euros. This was significantly lower than the cost of cholecystectomy before the changes were implemented (560 euros) ($P < 0{\cdot}01$). The costs decreased steadily throughout the study period. The decrease in the total cost of cholecystectomy resulted from a significant decrease in material costs, from 348 euros before the study to 59 euros in 2000 ($P < 0{\cdot}001$). There was an increase in labour costs between the control period (212 euros) and the study period (272 euros). This resulted from a small increase in the individual cost of each worker, particularly one surgeon whose status and salary changed in 1997. In the last 2 years the total operating room cost of an elective cholecystectomy was 330 euros or less.

Discussion

The results of this study suggest that the operating room cost of laparoscopic cholecystectomy can be lowered without altering the quality of surgery and clinical results. The cost was decreased by implementing changes that might reduce the cost of consumables. The complication rate was low and the length of hospital stay was short by French standards.

In France, surgeons tend to position the patient with both legs set apart[6,7]. The American position does not appear to make cholecystectomy more difficult. The surgeon and assistant are placed on the left side of the patient and the scrub nurse on the right side; this results in a minor economy. Intraoperative cholangiography can easily be carried out in this position. However, if CBD stones need to be extracted, it is better for the surgeon to stand between the patient's legs. This can now be implemented before operation in most cases.

There is a current trend towards open laparoscopy, which seems to be safer than creating a pneumoperitoneum after puncture with a Veress needle[8–11]. In addition, disposable Veress needles have to be used because reusable needles rapidly become blunt. Open laparoscopy may be difficult in obese patients. However, after gaining some experience, the authors found that it could be applied in all cases. Open laparoscopy can be performed in the left upper quadrant of patients who have an operative scar near the umbilicus.

It is now well known that reusable trocars and instruments are as safe as disposable ones[12–15]. The use of disposable trocars and instruments may be a source of considerable expense. It was never necessary to switch from using reusable trocars and instruments to disposable ones. In this department, the lifespan of 5- and 10-mm reusable trocars before repair is about 5 years. The lifespan of forceps, hooks and scissors is around 3 years without repair (about 5 years with repair)[12]. The lifespan of bipolar coagulation forceps is shorter.

Bipolar coagulation of the cystic artery avoided the need for clipping and was safe. No bleeding occurred after this procedure and 13·4 per cent of patients were day cases, which suggests that this is a reliable technique. Before bipolar coagulation is used, it is necessary to identify the artery clearly. This requires clear dissection of Calot's triangle and may be the best way to avoid accidental injury of the CBD or hepatic artery[16–18].

Intracorporeal ligation of the cystic duct avoided the use of a clip and was very cost-effective. Although this procedure requires training, it is now recommended for many laparoscopic procedures and should be taught during basic training[19,20]. As already reported[21], the procedure was quite safe. The only bile leak observed in this series of patients resulted from the failure to recognize an accessory duct in the gallbladder bed. There was no leakage from the cystic duct in any patient.

Disposable bags have been designed to extract resected specimens from the abdomen. They are convenient, but also quite expensive. However, it is fairly easy to introduce a surgical glove into the abdomen through the 10-mm trocar of the left upper quadrant and to put the gallbladder inside. In addition, the glove can be introduced between the liver and diaphragm to collect spilled stones if the gallbladder is ruptured during cholecystectomy. Difficulties in extracting the glove through the umbilical incision did not arise from the glove itself, but from the size of the gallbladder or the stones. Such problems may be minimized by emptying the gallbladder while in the glove, crushing the stones, or even slightly widening the aponeurotic and skin incisions.

It is always difficult to estimate medical costs. The purpose of this study was not to demonstrate that laparoscopic cholecystectomy is less expensive in the authors' department than in others, but to show whether it is possible to decrease the costs of a surgical procedure considerably without affecting surgical results. Approximately 68 000 laparoscopic cholecystectomies are performed every year in France[22]. The implementation of such changes should save approximately 15 million euros per year. The changes that have been implemented for laparoscopic cholecystectomy may be applicable to other laparoscopic procedures, such as gastro-oesophageal reflux surgery, colectomy or liver resection. Greater and greater demands to decrease costs will be made. Surgeons should anticipate economies before management does so blindly without any clinical evidence.

Acknowledgements

The authors thank Mrs Sylvie Glorian for assistance with data collection, and acknowledge the help of Dr Jacqueline Jeruss.

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Original article

All-comers policy for laparoscopic exploration of the common bile duct

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Background: Laparoscopic exploration of the common bile duct is associated with substantial variation in results suggesting that different patient populations are being reported. This report observes the results in a defined population and on an intention-to-treat basis.

Methods: All patients with suspected bile duct stones who were fit for surgery from April 1994 were offered laparoscopic bile duct exploration. There were 224 patients of mean age 56 years, of whom 174 were women. Endoscopic sphincterotomy was used in 149 patients deemed unfit for surgery. All data were recorded prospectively and checked at the time of discharge. Patients were followed up after 6 months and beyond after the operation.

Results: Stones were removed transcystically in 56 patients, transductally in 158 and by flushing in nine. The duct clearance rate was 96 per cent overall, 98 per cent for transcystic and 94 per cent for transductal exploration. Intracorporeal lithotripsy safely reduced the failure rate of exploration from seven of the first 28 to four of the subsequent 196 procedures. Biliary complications occurred in 16 per cent of procedures in which a T tube was used but only 4 per cent if the duct was closed by suturing. Conversion to open operation for severe gallbladder inflammation was necessary in 6 per cent of patients. There were no deaths, bile duct injuries or pancreatitis but complications occurred in 19 per cent, associated with use of T tubes and advancing age. Laparoscopic duct exploration succeeded in seven patients after previous cholecystectomy.

Conclusion: Laparoscopic bile duct exploration is effective and safe when used for all patients. For young and fit patients it should replace endoscopic sphincterotomy.

Paper accepted 3 September 2002

British Journal of Surgery 2002, **89**, 1608–1612

Introduction

Laparoscopic exploration of the common bile duct has not gained widespread popularity. The reported experience to date has been detailed elsewhere, together with reasons why it deserves greater consideration as a therapeutic tool[1]. Extraction of stones via the cystic duct is the most frequently used route. The rate of clearance of stones from the bile duct is reported to be from 75 to 98 per cent, with conversion rates of between 2 and 8 per cent. The reasons for conversion to open operation are usually related to difficult duct stones and only seldom relate to a difficult cholecystectomy. Complication rates are under 10 per cent in most series.

To assess the validity of laparoscopic bile duct exploration it is necessary to define the clinical context in which it is being used. To do this the patient selection criteria require definition so that selection bias and consequent clinical risk can be understood. This report describes the results of adopting a defined 'all comers' policy.

Patients and methods

All patients presenting with suspected bile duct stones to a single surgeon from April 1994, who were fit for operation, were treated with the intention of removing the gallbladder and bile duct stones laparoscopically. Very elderly patients, those unfit for surgery because of other medical problems and those with severe pancreatitis or cholangitis were treated by endoscopic sphincterotomy. Patients who had already had a sphincterotomy or previous cholecystectomy usually underwent endoscopic retrograde cholangiopancreatography if there was a suspicion of bile duct stones, but this position was modified later.

Laparoscopic cholecystectomy and bile duct exploration was undertaken using epigastric, right hypochondrial, right flank and umbilical ports. All operations were carried out by a consultant surgeon or trainee under supervision. Fluoroscopic operative cholangiography was performed selectively after preoperative screening until October 1999 and routinely thereafter. Intraoperative ultrasonography was performed for the detection of stones using a 7·5-MHz Aloka linear laparoscopic ultrasound probe (Key-Med, Southend, UK) as described previously[2]. Stones in the bile duct were measured using the 5-mm instruments on the cholangiogram as a measurement reference or with callipers on the ultrasound screen. Bile duct exploration was only carried out after positive demonstration of bile duct stones.

It was intended that all duct explorations be undertaken with a choledochoscope. Initially a 5-mm Pentax endoscope was used (Pentax, Slough, UK). Later in the series (after 72 patients) a 3-mm endoscope (Key-Med) was added, and both instruments were available routinely. A transcystic approach was used wherever feasible. Gentle bouginage was used occasionally but no forceful dilatation of the cystic duct. If a choledochoscope could not be passed down the cystic duct, or the bile duct stones were manifestly too large to be retrieved through the cystic duct, the transductal route was used via a longitudinal supraduodenal choledochotomy. Stone retrieval was undertaken with varying combinations of Dormia baskets, a 4-Fr Fogarty catheter, and by flushing the duct with saline. Large or impacted stones were fragmented under direct vision with an electrohydraulic lithotriptor passed down the choledochoscope channel (Wolf, UK). Clearance of the duct was assessed by passing the choledochoscope proximally and distally twice where possible. Postexploratory cholangiography was not used routinely. For the last 88 patients postexploratory ultrasonography was used. Occasionally, small stones were flushed out of the bile duct under radiographic control, with sphincter relaxation provided by intravenous hyoscine butyl bromide or glucagon. Following transductal exploration a 14-Fr latex T tube was placed, or the duct was sutured with interrupted 3/0 polyglactin sutures and a drain placed in the subhepatic space. Prophylaxis against infection was provided by a single perioperative dose of cefuroxime 750 mg, and against venous thromboembolism by a combination of compression stockings, intermittent pneumatic calf compression and subcutaneous heparin.

Clinical and operative details were recorded on a pro forma immediately after the operation. Postoperative complications and length of stay were added at the time of discharge. The data were then transferred to a computer database. Follow-up beyond 6 months was made by telephone contact.

To establish the additional morbidity of the duct exploration element of the operation, the outcome of these patients was compared with that of controls drawn sequentially from a laparoscopic cholecystectomy database of contemporaneous cases, matched for age, sex and mode of presentation.

Results

Two hundred and twenty-four patients of mean age 56 (range 17–90) years, 174 women, were treated. The presenting complaints are detailed in *Table 1*. Transcystic exploration was achieved in 56 patients (25 per cent). On eight occasions transcystic exploration removed some but not all of the stones and a transductal approach was required in addition. In nine patients it was possible to flush the stones through the biliary sphincter with or without a sphincter relaxant. One duct stone was left for later endoscopic sphincterotomy. The proportion of patients undergoing transcystic exploration rose from 21 to 37 per cent after the acquisition of a 3-mm choledochoscope in addition to a 5-mm endoscope, but this difference was not significant. Duct stones were cleared in 96 per cent of patients overall, 98 per cent transcystically and 94 per cent transductally. These results include the procedures converted to open operation detailed below. An analysis of the results after the first 28 operations showed that impacted stones were a cause of failure. Thereafter, lithotripsy was used on 31 occasions and the rate of failure to clear the duct without conversion or later endoscopic sphincterotomy fell from seven of the first 28 procedures to four of the subsequent 196 ($P < 0.001$, χ^2 test). There were no complications related to the use of lithotripsy. The mean stone size was 8·4 mm and the relation to route of exploration is shown in *Fig. 1*.

In 53 cases the bile duct was closed around a T tube. This was the preferred method originally but, of the first 44 patients, seven suffered bile leakage around or displacement of the T tube. Direct suture closure was subsequently adopted, leaving the use of a T tube for patients with marked cholangitis and technically difficult cases only. There were four biliary complications only in the suture closure group, all of which were bile leaks through the subhepatic drain that were prolonged beyond 3 days. This reduction in

Table 1 Clinical presentation of patients undergoing transcystic and transductal bile duct exploration

	Transcystic	Transductal
Biliary colic	25	64
Jaundice	23	71
Pancreatitis	7	14
Cholecystitis	0	4
Cholangitis	1	5

biliary complications was statistically significant ($P = 0{\cdot}015$, χ^2 test with Yates' correction). There was no difference in the non-biliary complications such as atelectasis between the two methods of duct closure, even though patients in the suture closure group were older.

Conversion to open operation was required on 29 occasions (13 per cent). The reasons are detailed in *Table 2*. For difficult bile duct stones, four of the five conversions took place before the use of lithotripsy, whereas for severe inflammatory fibrosis the cases were spread throughout the series and represented 6 per cent of the whole. The mean age of patients whose procedure was converted was 57 years, similar to that of the remaining patients. There was no excess of jaundiced patients or those who suffered complications in the group converted. Operations in men were converted more often than those in women (16 *versus* 12 per cent) but the difference was not significant.

There was one negative exploration based on a false-positive cholangiogram. It is possible that a stone was passed through the sphincter during the initial flushing of the bile duct during choledochoscopy. Failure to clear the duct at the initial operation occurred in seven patients. In one a stone was deliberately left for later endoscopic sphincterotomy. In two the stones were impacted and were removed by later endoscopic sphincterotomy. On three occasions fragments of stone were missed and were removed endoscopically, and on one occasion a stone was missed on operative cholangiography; the latter stone was also removed endoscopically. Five of these seven patients were among the first 50 in the series. Four had undergone transductal and two transcystic operation.

Intraoperative complications occurred in seven patients (3 per cent) (*Table 3*). Postoperative complications occurred in 44 patients (19 per cent) (*Table 3*). There were no deaths and no bile duct injuries, postoperative pancreatitis or thromboembolic complication. There was no difference in the preoperative bilirubin level between those with and without complications. Patients experiencing 'pathological' (atelectasis, cardiac arrhythmia, urinary retention, etc.) as opposed to 'mechanical' (T-tube problems, etc.) complications had mean age of 71 years ($P < 0{\cdot}001$, Student's t test) compared with 54 years for patients who had no complications. Three further interventions were required: laparoscopic drainage of a bile collection, transanal drainage of a pelvic abscess and repair of a port-site hernia. The difference in the number of complications between transcystic and transductal exploration was significant ($P = 0{\cdot}02$, χ^2 test).

The postoperative length of stay is shown in *Table 4*. All these results include the procedures that were converted to open operation so they are presented on an 'intention to treat' basis.

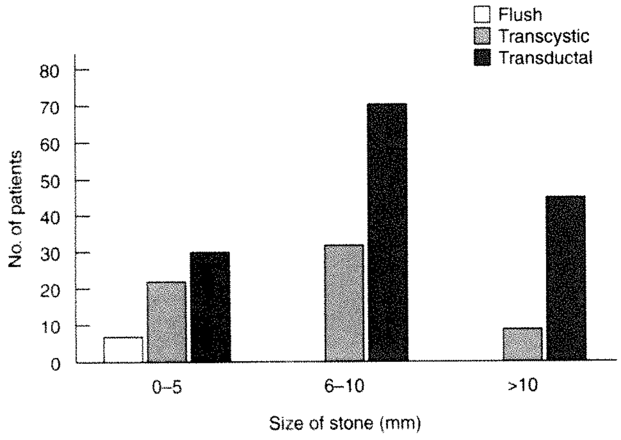

Fig. 1 Size of stone and route of exploration

Table 2 Conversions to open operation

	No. of patients
Severe gallbladder inflammation	14
Impacted stones before lithotripsy introduced	4
Impacted stones after lithotripsy introduced	1
Very large number of stones for choledochoduodenostomy	3
Bleeding	4
Difficult access to common bile duct	3

Table 3 Complications

	No. of patients
Intraoperative	
Stone and basket impacted during transcystic exploration	2
Bougie perforation of cystic duct	1
Dropped suture needle (recovered)	1
Needle perforation of posterior wall of bile duct	1
Apparent ischaemia of segment 3 of liver	1
Operation abandoned owing to obesity	1
Postoperative	
T-tube related	7
Prolonged bile leak	4
Chest infection	8
Atelectasis	6
Cardiac arrhythmia	3
Retention of urine	5
Urinary infection	4
Pyrex of unknown origin	3
Pelvic abscess	1
Port-site hernia	1
Clostridium difficile infection	1
Wound infection	1

Table 4 Comparison between matched controls undergoing laparoscopic cholecystectomy and two forms of laparoscopic duct exploration

	Transductal exploration	Matched cholecystectomy	Transcystic exploration	Matched cholecystectomy
Postoperative complications (%)	17	9	9	3
Postoperative stay (days)	4·8	1·9	2·0	1·5
Conversion (%)	17	7	4	7

Matched patients undergoing laparoscopic cholecystectomy alone had a significantly lower morbidity rate and length of stay but not conversion rate compared with those who underwent transcystic exploration (*Table 4*). Transductal exploration was associated with a significantly higher morbidity rate, rate of conversion to open operation and a greater length of stay than cholecystectomy in matched patients. Cardiorespiratory complications in the transcystic group with the addition of impacted stones and severe gallbladder fibrosis in the transductal group accounted for these differences. Delay in discharge was particularly associated with the use of a T tube.

Follow-up after 6 months postoperatively was achieved in 88 per cent of patients and no missed stone was detected. Two patients had biliary malignancy.

Seven duct explorations were completed in patients who had undergone previous cholecystectomy, one open and six laparoscopic. The same port sites and approach to the common bile duct were used. There were no conversions to open operation and no intraoperative or postoperative complications.

Using the selection criteria described above, another 149 patients had duct stones treated by endoscopic sphincterotomy in the same time period.

Discussion

Laparoscopic exploration of the common bile duct is an effective and relatively safe method of removing bile duct stones for patients who are fit for operation. The proportion of patients treated transcystically in this series was only 25 per cent, rising to 26 per cent if the patients whose stones were flushed out are included, compared with an average of 71 per cent in the literature. This relates not so much to the size of the stone but to the size and configuration of the cystic duct in relation to the choledochoscope. The addition of a 3-mm choledochoscope had a marginal benefit. Choledochoscopy was chosen as the method for exploration because it allows removal of stones and lithotripsy under direct vision. Previous studies have suggested that it is also the best way of ensuring a clear duct[3,4]. Others use radiological exploration with a Dormia basket under radiographic control. The basket in some cases is passed through the ampulla and cases of pancreatitis have been noted[5]. In this study particular care was taken to avoid instrumentation of the ampulla if at all possible and pancreatitis as a complication was avoided.

None of the reported studies particularly highlights difficulty with impacted stones and the results of treating them, although they have been noted and been a cause for conversion to open operation. Impacted stones were a large problem early in the present experience. The use of intraluminal electrohydraulic lithotripsy deals easily and effectively with the difficult stone impacted in the bile duct or, particularly, the ampulla. Ido *et al.*[6] used lithotripsy to fragment and then flush stones through the ampulla without retrieving any fragments, but this resulted in complete clearance in only 51 of 81 patients. Paganini and Lezoche[7] and Berthou *et al.*[8] have also used this technique. In the present study it was found to be less satisfactory if used to fragment large but mobile stones, in which case a large choledochotomy and balloon trawling of the duct was more effective.

There has been relatively little emphasis on the best way to deal with the bile duct after choledochotomy. T tubes are associated with significant complications. This problem has been noted by Martin *et al.*[9], who reported a complication rate of 16 per cent following the use of T tubes, the same as the present rate of 16 per cent. Direct suture closure of the bile duct has been much more effective, reducing biliary problems to 5 per cent without the need for reintervention. This is similar to the findings of the randomized trial of Williams *et al.*[10], in which the use of T tubes was associated with greater morbidity than suture closure of the bile duct following open bile duct exploration. The use of T tubes should now be reserved for patients with purulent cholangitis and where there is technical difficulty with the biliary tree, such as a patent duct of Lushka.

Marked fibrosis necessitated conversion in a surprisingly large number of patients, twice that for laparoscopic cholecystectomy alone. This difficulty has not been highlighted previously but occurred in 3 per cent of the laparoscopic explorations reported by Millat *et al.*[11]. Sabharwal *et al.*[12] noted that patients with bile duct stones had a more difficult open cholecystectomy and Amorri *et al.*[13] showed that a previous sphincterotomy predicted a more difficult cholecystectomy. Stoker[14] described conversion to open cholecystectomy in 11 of 80 patients in order to complete removal of the gallbladder. The present authors found excessive fibrosis in the gallbladder in patients with duct stones which was thought to be due to obstruction[15]. This high conversion rate continues to be a problem and one which is difficult to overcome. It occurs more often in patients with jaundice at the time of the operation.

In this series there was a low rate of transcystic exploration, a high incidence of impacted stones and the need for an adjunct to remove them, and a persistently high conversion rate for gross gallbladder inflammation compared with that of other authors. There is evidence that surgeons may be selective in their use of laparoscopic bile duct exploration (or that the selection is carried out before patients are referred for cholecystectomy). Choledochoscopic lithotripsy does not occur until the number in any series rises to well over 100 cases[7,8]. Halpin *et al.*[16] recently reported the results of laparoscopic ultrasonography in a consecutive series of 394 laparoscopic cholecystectomies. Thirty-nine patients had bile duct stones with a mean diameter of 2·4 mm, substantially smaller than the mean of 8·4 mm in this series when the same measurement technique was applied. The explanation for varying results probably lies therefore in the selection of patients and the population from which they are derived.

For fit, young patients with bile duct stones, laparoscopic exploration of the common bile duct is an excellent treatment, with its high efficacy, minimal complication rate and preservation of the biliary sphincter. There is a clear argument for not using endoscopic sphincterotomy in these patients. In older patients the best treatment remains uncertain. The propensity to complications in the elderly has been highlighted for laparoscopic cholecystectomy alone[17] and was observed in the present matched series of control cholecystectomies. As bile duct stones represent a greater proportion of gallstone disease in the elderly[18], and there are advantages in removing the duct stones and gallbladder in such patients[19], there is clearly a need for further study in this group.

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Laparoscopic *in situ* ablation of liver cancer with cryotherapy and radiofrequency ablation

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Background: *In situ* ablation has potential for the treatment of patients with liver cancer either as a single-modality treatment or in combination with liver resection.

Methods: Laparoscopy and intraoperative ultrasonography was used to target cryotherapy and radiofrequency ablation. Thirty-eight patients with 146 liver lesions were treated between January 1995 and December 2000 using cryotherapy alone (nine patients), combined cryotherapy and radiofrequency (eight), radiofrequency alone (15) and *in situ* ablation with liver resection (six). Cancers treated were metastases from colorectal tumours ($n = 25$), hepatocellular carcinoma ($n = 5$), and neuroendocrine ($n = 5$), melanoma ($n = 2$) and renal cell ($n = 1$) metastases. Complications and survival after *in situ* ablation were compared with age- and disease-matched controls treated with systemic chemotherapy.

Results: The mean age was 61·6 years. At mean follow-up of 26·6 (range 3–62, median 26) months, 22 patients were alive. Survival was increased following *in situ* ablation compared with that in controls ($P < 0·001$). Local recurrence at the ablation site was noted in 12 of 44 lesions following cryotherapy and in 20 of 102 lesions after radiofrequency ablation, and new disease in the liver was found in six of 17 and six of 29 patients respectively. The complication rate was higher with cryotherapy than with radiofrequency ablation (four of 17 *versus* one of 29). Intraoperative ultrasonography identified 14 new hepatic lesions (10 per cent) not seen on preoperative imaging.

Conclusion: Laparoscopic *in situ* ablation should include ultrasonography to stage the disease. *In situ* ablation appears to have a survival benefit and should be considered for the treatment of liver cancer in appropriate patients.

Paper accepted 12 July 2002

British Journal of Surgery 2002, **89**, 1613–1619

Introduction

Surgical resection remains the 'gold standard' treatment for primary and secondary liver cancer[1–4]. However, severe coexistent liver disease may preclude resection of primary liver cancer, and the pattern of disease, with multiple deposits, often prevents curative resection in patients with secondary disease[5]. Given the limitations of resectional surgery, and the poor response of liver cancer to modalities such as radiotherapy and chemotherapy, there is increasing interest in *in situ* ablation therapy for the treatment of liver tumours[6–9].

In situ ablation can be delivered using minimal-access techniques, and as such is better tolerated and associated with fewer side-effects than traditional surgical resection. To date these interstitial ablation techniques have used chemical treatment (alcohol)[10], cold (cryotherapy)[11–14], heat (radiofrequency, microwave, laser)[12,15] and drugs (chemoembolization, photodynamic therapy)[16,17] to achieve *in situ* tumour destruction. All of these emerging techniques have the ability to treat recurrent disease irrespective of previous treatments. Interstitial ablation of liver cancer has significant potential not only as a first-line primary treatment modality, but also as a second-line treatment in appropriately selected patients.

For these techniques to have a positive impact on patient outcome, it is essential that the disease is staged accurately and that all macroscopically diseased tissue is adequately ablated with the chosen treatment. The techniques of cryosurgical[14] and radiofrequency[18] ablation have been adapted for use with a laparoscopic approach, to combine the advantages of accurate disease staging with intraoperative ultrasonography, rapid procedure recovery and ease of repeat treatment when necessary. This study presents the authors' experience with laparoscopic cryotherapy and radiofrequency ablation for the treatment of liver cancer over the period from January 1995 to December 2000.

Patients and methods

Demographic data

Between January 1995 and December 2000, 38 patients with liver cancer were treated with cryotherapy and/or radiofrequency ablation in Ninewells Hospital and Medical School, Dundee. Twenty-two patients were men and 16 were women; the mean age was 61·6 (range 24–79, median 65) years. A total of 146 lesions was treated by interstitial ablation. Nine of 38 patients were treated with cryotherapy alone, 15 with radiofrequency ablation alone, eight received a combination of cryotherapy and radiofrequency ablation, and six had a combination of surgical resection and radiofrequency ablation (open surgery).

Pathology of liver lesions ablated

Liver metastases from a primary colorectal tumour were the predominant cancers in this patient population ($n = 25$). Nine patients in this group were noted to have synchronous metastases at the initial colorectal cancer resection. Patients with synchronous disease had full liver imaging by computed tomography (CT) or magnetic resonance imaging (MRI) at 3 months after the primary operation, and were then scheduled for *in situ* ablation. Other lesions ablated included hepatocellular carcinoma ($n = 5$), neuroendocrine metastases ($n = 5$), malignant melanoma with liver metastases ($n = 2$) and renal cell carcinoma metastases ($n = 1$).

In situ ablation therapy

During the study period 147 patients with liver cancer were considered for *in situ* ablation; 38 (26 per cent) met the eligibility criteria. Inclusion criteria were defined as a total tumour load of 30 per cent or less of total liver volume (calculated by volumetric analysis on preoperative staging MRI), five or fewer lesions, and maximum single lesion diameter 8 cm or less for metastases from colorectal cancer. An 8-cm lesion required treatment with cryotherapy to ensure a 10-cm diameter ablation sphere (which destroys approximately 523 cm^3; volume $4/3\pi r^3$). Metastatic neuroendocrine tumours were debulked regardless of lesion number (range 6–9). Patients with lesions smaller than 5 cm were treated with radiofrequency ablation, and those with lesions greater than 5 cm received cryotherapy. Eight patients with multiple lesions of mixed size were treated with a combination of cryotherapy and radiofrequency ablation. Additional exclusion criteria that precluded interstitial ablation were non-correctable low platelet count (less than 100×10^9/l) or coagulopathy, and Child's grade C cirrhosis.

Cryosurgical ablation therapy

The technique has been described[14]; briefly, laparoscopy and adhesiolysis is followed by intraoperative ultrasonography to stage the disease. Additional ports are placed for insertion of cryo-needles, which are 50 or 100 mm in length and 2 or 3 mm in diameter at the active tip. Three needles can be placed simultaneously into a single large lesion, or three small separate lesions may be treated simultaneously. Each treatment consists of a 20-min freeze–thaw cycle using thermocoupling to monitor ablation temperatures at the needle tip (Spembly Medical, Andover, UK). The needles are cooled by liquid nitrogen and typically reach −190°C. The size of the circumferential ice-ball is monitored by sonography, and ablation continued to ensure an adequate margin of 1 cm beyond the tumour. During cryoablation warm saline is irrigated on to the suprahepatic inferior vena cava to minimize heat loss from the patient and prevent a reduction in body temperature.

Radiofrequency ablation

Laparoscopy and ultrasonography are employed first to stage the disease, then sonography is used to guide radiofrequency needle placement[18]. Initial experience was with the RITA® system (RITA® Medical Systems, Mountain View, California, USA), but from 1997 the water-cooled Radionics™ system (Tyco Healthcare, Gosport, UK) was used to achieve a greater ablation diameter. For lesions up to 3 cm in diameter the single-needle device is adequate, but the triangular three-needle 'cluster' configuration is recommended for lesions of 3–5 cm in diameter, and for lesions with a maximum diameter of 5–8 cm in patients not suitable for cryoablation. Each ablation is achieved using 100 W of high-frequency alternating current (2 A) for at least 720 s. Lesions greater than 3 cm in maximum diameter require multiple overlapping ablation zones, each of 720-s duration. At the end of each ablation period the temperature of the needle tip is monitored, and should remain above 60°C for 1 min to reflect an adequate ablation.

Lesion ablation for both cryotherapy and radiofrequency ablation is monitored by intraoperative ultrasonography. During cryoablation the ice-ball forms a highly visible hyperechoic rim with posterior acoustic shadowing. This hyperechoic rim is monitored in real time as it advances into and beyond the lesion[19]. With radiofrequency ablation the nitrogen micro-bubbles that are generated by tissue heating are visualized on sonography as a hyperechoic sphere that gradually expands out from the needle as the ablation process progresses[20]. All intraoperative and postoperative complications (and deaths within 30 days) were collected prospectively.

Patient follow-up

Postablation surveillance consisted of determining serum α-fetoprotein and carcinoembryonic antigen levels at 3-month intervals, and liver-specific CT or MRI at 3–6-month intervals. Patient survival is presented as a Kaplan–Meier survival curve tested for significance with the log rank test. This was a non-randomized phase 2 study, and therefore for comparison of outcome in the colorectal cancer group only survival was compared with that of a similar patient population treated with systemic chemotherapy.

Colorectal cancer control group

Eighteen patients with hepatic metastases from primary colorectal cancer were age-, sex- and stage-matched with patients with colorectal cancer treated by *in situ* ablation. Inclusion criteria for selection of control patients were identical to those for *in situ* ablation therapy (no extrahepatic disease, five or fewer lesions, and maximum single lesion diameter of less than 8 cm). Mean age of the control group was 66·6 (range 52–77, median 68·5) years. Six of the 18 patients in the control group and nine of the 25 in the *in situ* ablation group were treated for synchronous hepatic metastases.

The regimen used for palliative systemic chemotherapy was determined by the medical oncologist. Patients who had not previously had chemotherapy ($n = 11$) received 5-fluorouracil (5-FU) and folinic acid every 3 weeks for six cycles. The dosage of each drug was adjusted according to body size. Women received 280–350 mg folinic acid plus a 550–700-mg 5-FU bolus, followed by a 850–1100-mg 5-FU infusion over 48 h. Men received 300–350 mg folinic acid plus a 600–800-mg 5-FU bolus, followed by a 900–1200-mg 5-FU infusion. Two patients withdrew from chemotherapy after one cycle of treatment, two withdrew after two cycles, and one after four cycles.

Seven patients who had previously received 5-FU-based adjuvant chemotherapy were offered irinotecan 350 mg/m^2 via a 60-min infusion every 3 weeks for six cycles. One patient withdrew after a single cycle, and another after three cycles of treatment.

Results

At the end of December 2000, 22 of 38 patients were alive and continued in the surveillance programme, whereas 15 patients had died as a result of progression of cancer, and one patient died in the perioperative period from complications of cryotherapy. The mean follow-up from the date of ablation therapy was 26·6 (range 3–62, median 26) months.

Thirty of the 38 patients had a single ablation treatment only, 13 had two treatments, and one patient had three treatments for recurrent disease within the liver. Three patients developed extrahepatic disease after the initial interstitial ablation and underwent no further treatment.

Most patients (19 of 38) had a single lesion ablated, six patients had two lesions ablated, five had three lesions ablated, three had four lesions ablated, and one patient had five lesions ablated. Four patients with metastatic carcinoid had more than four lesions ablated (range 6–9) as a debulking procedure because anatomical resection was not feasible.

Thirteen patients with colorectal cancer (53 per cent) required a second ablation treatment, and three patients required a third ablation for recurrent cancer at the site of previous ablations or for new metastatic deposits within the liver. Overall 14 of 25 patients (56 per cent) with colorectal cancer developed further disease within the liver during follow-up.

Disease staging

The 38 patients underwent 59 ablation sessions. Intraoperative ultrasonography identified 14 liver lesions (10 per cent of the total 146 lesions) that were not seen with preoperative MRI. On retrospective analysis of the MRI scan, it was not possible to identify these lesions. Occult metastases were typically of small diameter (less than 10 mm), subcapsular and adjacent to (or near) the falciform ligament. The distribution of occult hepatic deposits is shown in *Table 1*.

Procedure-related complications

Most complications were associated with cryotherapy and these occurred in proportion to the volume of liver parenchyma ablated. Intraoperative complications were identified in 19 of 44 cryoablation sessions. Liver fracture or cracking occurred in 15 of 44 cryotherapy ablations, and required treatment with fibrin glue and/or argon plasma coagulation. Hypothermia and a nitrogen burn to the skin occurred in one patient each. There were no procedure-related complications in 25 of 44 cryoablations.

Postoperative complications with cryotherapy were identified in four of 17 patients. Most common was thrombocytopenia, which occurred in three patients that required treatment with platelet transfusions and fresh frozen plasma. One patient died from multiorgan failure following cryoablation of an 8-cm lesion. This patient had thrombocytopenia that failed to respond to platelet and plasma transfusion. Right lower lobe pneumonia and pleural effusion occurred in one patient each, but both patients recovered fully with appropriate treatment.

Complications associated with radiofrequency ablation were infrequent and of low morbidity (*Fig. 1*). One patient complained of right-sided abdominal pain associated with mildly deranged liver function. This required treatment for 72 h with opioid analgesia, and resolved thereafter. Ultrasonography at 1 week failed to identify pathology (e.g. abscess) within the liver, and the patient remained asymptomatic thereafter.

Table 1 Hepatic distribution of occult lesions identified at laparoscopy but not seen on preoperative magnetic resonance imaging

Liver segment	No. of occult lesions
I	1
II	3
III	5
IV	3
V	1
VI	1
Total	14*

*Represents 10 per cent of all lesions treated by *in situ* ablation

Tumour recurrence and patient survival

Twenty-two of the 38 patients treated by *in situ* ablation were alive and 16 had died at a mean follow-up of 26 months. Recurrence at the previous ablation site was 28 per cent (12 of 44 lesions) for cryoablation and 20 per cent (20 of 102 lesions) for radiofrequency ablation. Cancer recurrence within the liver at a remote site was noted in 35 per cent (six of 17 patients) following cryotherapy and in 20 per cent (six of 29 patients) after radiofrequency ablation (*Fig. 1*). The mean survival for all patients treated with *in situ* ablation was 26·1 (range 3–62) months, and 29·6 (range 10–45) months for those treated with a combination of cryotherapy and radiofrequency.

The overall survival of patients with colorectal cancer treated by *in situ* ablation was greater than expected. A non-randomized comparison with an age- and disease-matched control group of patients with colorectal tumours treated with systemic chemotherapy during the same time period (1995–2000) showed a significant difference in survival. Kaplan–Meier survival curves demonstrated increased survival in the *in situ* ablation study group compared with the chemotherapy control group ($P < 0·001$) (*Fig. 2*). Mean survival following systemic chemotherapy was 8·8 (range 1–27, median 7·5) months, which was not significantly better than survival in patients receiving no active treatment.

A similar survival benefit was noted in patients with colorectal cancer whether treated with a combination of cryotherapy and radiofrequency ablation (n = 8), radiofrequency ablation alone (n = 10) or cryotherapy alone (n = 7) (*Fig. 3*) when compared with the chemotherapy group (n = 18).

It is not possible to comment on the survival advantage associated with interstitial ablation for the 13 patients

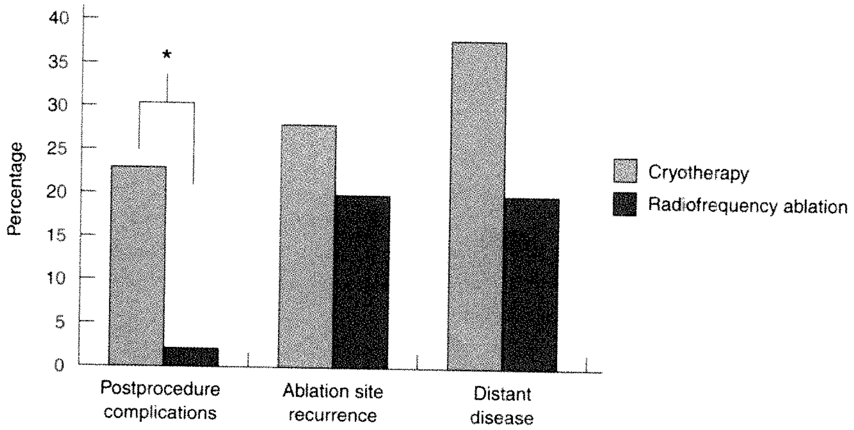
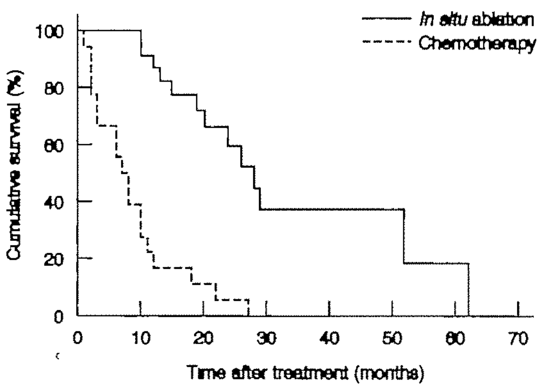
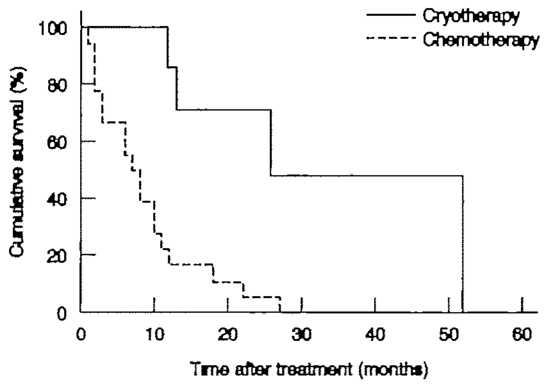


Fig. 1 Postoperative complications, ablation site recurrence and disease recurrence after *in situ* ablation of liver cancer with cryotherapy (17 patients, 44 lesions) and radiofrequency ablation (29 patients, 102 lesions). *P = 0·01 (two-tailed Student's t test)



No at risk						
In situ ablation 25	21	12	5	2	2	1
Chemotherapy 18	4	1	0	0	0	0

Fig. 2 Kaplan–Meier survival curves for patients with liver metastases from colorectal cancer who received *in situ* ablation or chemotherapy (controls). $P < 0.001$ (log rank test)



No at risk							
Cryotherapy	7	6	4	3	2	1	0
Chemotherapy	18	4	1	0	0	0	0

Fig. 3 Kaplan–Meier survival curves for patients with liver metastases from colorectal cancer who received cryotherapy or chemotherapy (controls). $P < 0.001$ (log rank test)

without colorectal cancer in this study, because the sample size for each tumour type was too small. However, the overall survival of these patients treated by *in situ* ablation was significantly longer than that of patients treated for colorectal cancer metastases. Similarly, it is premature to comment on the long-term survival of the six patients who had radiofrequency ablation of small deposits in segments II or III, in combination with classical right hepatectomy for extensive disease in the right lobe.

Discussion

There is no doubt that surgical resection is the 'gold standard' for the curative treatment of liver cancer. However, because few patients are suitable for radical surgery, there is a need to explore alternative therapeutic modalities such as those offered by interstitial or *in situ* ablation. Ideally these interstitial techniques of cancer ablation should be as effective as curative operation. However, even a modest improvement in survival compared with other palliative therapies would be advantageous, as chemotherapy achieves a survival benefit of only a few months in most patients[21–24].

A variety of *in situ* ablation techniques is currently under evaluation, and most can be used with minimal-access delivery systems. Within the authors' unit, the potential of cryotherapy ablation and radiofrequency ablation using laparoscopy to stage disease and target therapy has been explored. Traditionally cryotherapy has required a laparotomy to place the needles and deliver therapy[25], and thus the advantage of a laparoscopic approach is primarily a reduction in access trauma. Intraoperative and postoperative complications are proportional to the total ablation or freeze volume, and this is unaffected by the access route.

However, laparoscopic staging combined with ultrasonography is widely recognized as the most accurate method currently available for staging of oesophagogastric, hepatobiliary and pancreatic cancers. This was reflected in this study, where 10 per cent more disease was identified at laparoscopy than with preoperative imaging. Clearly such lesions would be missed if a percutaneous approach were used for targeting radiofrequency ablation. Others have reported a similar experience with laparoscopic staging before *in situ* ablation in the liver[9,12,26,27]. While there are clear benefits in disease staging with operative ultrasonography, general anaesthesia is required in all patients.

This study was not a prospective randomized trial, but it is interesting to note the increased survival in patients treated by interstitial ablation, particularly given that tumour recurrence was noted in 32 of 146 lesions at the ablation site, and distant recurrence was observed within the liver in 12 patients. The higher recurrence rates associated with cryotherapy are not altogether surprising in view of the fact that this modality was used to treat larger lesions. Selection criteria are important when considering patients for *in situ* ablation, as clearly a positive impact on patient survival can be achieved only by treatment of all macroscopic disease. Thus interstitial ablation is not suited to all, and indeed only 26 per cent of patients referred to the authors' unit were deemed suitable for these therapies. Similar ablation site recurrence rates have been reported by others[9,12,28,29]. Ablation site recurrence clearly reflects an inadequate initial tumour ablation and remains the Achilles' heel of interstitial ablation techniques. This failure may be due to an insufficient tumour ablation zone as a result of poor tissue penetration or inaccurate radiological monitoring of the ablation process.

Most patients with liver cancer in the UK have metastatic disease from a primary colorectal cancer. Given the stringent selection criteria for both resectional surgery and *in situ* ablation, it is estimated that up to 35 per cent of patients with colorectal cancer metastases confined to the liver may ultimately be suitable for surgical intervention.

One major advantage of *in situ* ablation is the relative ease with which recurrent disease (following previous liver resection) can be targeted and treated, and this application is likely to develop significantly over the next few years[30]. Another area of increasing interest is that of combining interstitial ablation techniques with resectional surgery for metastatic disease, and this too has the potential to increase the numbers of patients suitable for surgical intervention[31–34].

In conclusion, this study has demonstrated that both cryotherapy and radiofrequency ablation are suitable for laparoscopic treatment of liver cancer, and ablation can be achieved with reasonable morbidity and mortality. Laparoscopic staging is highly sensitive, and *in situ* ablation of colorectal cancer liver metastases appears to be associated with a survival advantage in selected patients. Further prospective randomized studies of these modalities are clearly warranted.

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Differences in clinical performance (*Br J Surg* 2002; 89: 948–9)

Sir

One factor that may determine different outcomes between surgeons, which never seems to be considered specifically, is case selection, or practice style. Physicians, and occasionally general practitioners, often know to which surgeon to refer the marginal case because they know that surgeon will 'always operate on anything'. This factor may not necessarily be identified by case mix or risk assessment and I suspect it may be as potent a cause of poor performance as suboptimal surgical technique.

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Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy (*Br J Surg* 2002; 89: 752–6)

Sir

Radiofrequency ablation (RFA) of liver tumours may be a useful adjuvant therapy for relapsed disease within the liver; however, it has not been shown to be curative in long-term studies. Repeat hepatectomy can provide long-term survival rates similar to those of first hepatectomies, with no mortality and comparable morbidity[1]. A 5-year survival rate of 32 per cent is described for repeat hepatectomy for colorectal liver metastases[2].

There are several problems with RFA not encountered with surgery. These are generally related to dependence on the limitations of current extracorporeal imaging to diagnose and localize disease accurately. In the present series of RFA, the authors have excluded patients with extrahepatic recurrence, but how was the extrahepatic disease confirmed? Was laparoscopy carried out in all cases, as peritoneal disease is difficult to diagnose using radiological investigations? In their mixture of recurrent liver tumours a large subset were hepatocellular tumours; how were these confirmed as carcinomas as opposed to cirrhotic regeneration nodules? Preoperative biopsy of lesions is to be avoided as this disseminates disease, and RFA can do the same[3]. The overall accuracy of imaging by any modality is only about 45 per cent when patients come to operation and this is inadequate for planning potentially curative percutaneous treatments[4].

The authors compare survival data following RFA with a historical series of patients who had repeat hepatectomy but, as they state, the 28 patients with recurrent tumours not suitable for RFA underwent reresection. Thus, it is obvious that the patients who underwent RFA were a selected subgroup with low-volume disease and thus their survival cannot be compared with that of the surgery group. Failure of local treatment may manifest itself by dissemination rather than local progression, rendering patients incurable by salvage surgery. The 5-year survival data on recurrent liver tumours treated by RFA are not available and in the long-term RFA may not be as effective as repeat hepatectomy.

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Botulinum neurotoxin and other treatments for fissure-*in-ano* and pelvic floor disorders (*Br J Surg* 2002; 89: 950–61)

Sir

This review is a valuable summary of the state of research of botulinum neurotoxin used in the treatment of disorders of the lower gastrointestinal tract; however, the authors did not mention the first publication that described the application of botulinum neurotoxin for the treatment of chronic anal fissure (CAF)[1]. The authors, referring to their work published in 2002, report that higher doses led to an improved success rate. In my experience higher doses (50 units botox) can affect the outcome of treatment for CAF[2].

The authors also did not refer to this paper when stating that topical nitrates potentiate the effect of botulinum neurotoxin[2]. The authors' opinion that injection of botulinum neurotoxin into the external anal sphincter (EAS) is not yet the first-choice treatment for CAF is not convincing. Jost[3] injected botulinum neurotoxin into the EAS in 100 patients and showed its high efficacy for CAF. Others have shown similar, or higher, efficiency using even larger doses[4]. It is widely known that botulinum neurotoxin is a safe and effective method of treating CAF, even if doses higher than those administered by Jost are used.

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Authors' reply

Sir

Botulinum toxin injected into the external anal sphincter (EAS) is also effective for treating chronic anal fissure (CAF). However, CAF is associated with spasm of the internal anal sphincter (IAS), and the rationale for injecting botulinum toxin into the EAS is therefore unclear. We found that toxin injected into the IAS did not spread to the EAS, and we believe that it is easier to inject the toxin directly into the IAS[1]. The role of EAS weakening in the treatment of CAF remains uncertain (healing rate approximately 80 per cent and up to 80 per cent, depending on whether toxin was injected into the EAS or the IAS respectively). Regarding the therapeutic effect of botulinum toxin injection and local application of nitrate or botulinum toxin alone, 30 consecutive patients with anal fissure were studied. It has been documented that combined botulinum toxin injection and local application of nitrate was more effective than botulinum toxin alone[2]. Furthermore, higher doses are not necessary (of 13 patients with chronic anal fissure who received 50 units botulinum toxin, no healing was reported in six)[3], as we were able to produce an adequate effect using lower doses. Higher doses will increase costs, and may contribute to the incidence of undesired effects.

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Retrospective study of acute toxicity following short-course preoperative radiotherapy (*Br J Surg* 2002; 89: 889–95)

Letter 1

Sir

It is still unclear whether patients with tumour node metastasis (TNM) stage IV rectal cancer benefit from preoperative radiotherapy. There is no evidence to suggest that these patients 'could be spared potential toxicity of short-course preoperative radiotherapy'. In the cited Dutch total mesorectal excision (TME) trial[1] radiotherapy had no effect on local recurrence in patients with stage I and IV disease in a univariate analysis, but in multivariate analysis no significant interaction was found between the TNM subgroup and treatment effect. In fact, patients with distant disease who received radiotherapy had a 10·1 per cent local recurrence rate at 2 years *versus* 23·8 per cent for patients who had no radiotherapy. Lack of statistical significance of this difference may be related more to small sample size than to ineffectiveness of the radiotherapy. The randomized controlled trials to date[1–3] do not provide definitive conclusions about use of radiotherapy in patients with metastatic disease, mainly because such patients are not enrolled in trials if identified before operation. However, there are at least two subgroups of patients with distant disease who may benefit from radiotherapy: patients with resectable distant disease and those in whom control of metastases can be achieved with local ablative techniques.

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Letter 2

Sir

Toxicity with this multimodality therapy is a major concern, but which modality dominates the toxicity – surgery or radiotherapy? It would be useful to evaluate acute radiation toxicity by applying a validated scoring system, such as the Common Toxicity Criteria[1] or Radiation Therapy Oncology Group scales[2]. Permanent radiotherapy toxicity may be due to persisting acute reactions[3]. The authors report a 9 per cent mortality rate within 3 months of commencing radiotherapy, but do not include the causes. In our series[4] we have treated 43 patients with rectal cancer and have encountered no radiation-related mortality. Surgery should be performed within 7 days of radiotherapy to avoid downstaging the tumour and excess cardiovascular mortality. Patients who are downstaged from node positive to node negative tend to have a worse outlook than genuinely node-negative patients. In this study, the median interval between radiotherapy and surgery was nearly 2 weeks. Is it possible that the poor prognosis tumours were hidden by this downstaging effect? We also found a significantly higher incidence of long-term toxicity in patients with tumours of the lower third of the rectum.

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Authors' reply

Sir

We thank Prabhudesai *et al.* for highlighting the difficulty in determining which modality is responsible for toxicity following multimodality treatment. It was our intention to document all postoperative complications, regardless of cause. Of the 15 patients (9 per cent) who died within 3 months of commencing short-course preoperative radiotherapy, the causes of death were septicaemia (five), pneumonia (three), cardiovascular events (two), pulmonary embolus (two), gastrointestinal haemorrhage (one), small bowel obstruction (one) and unknown (one). As this was not a randomized trial comparing short-course preoperative radiotherapy followed by surgery with surgery alone, it would not be possible to relate a particular complication to a specific modality. Equally, the above statement applies to their study of 43 patients[1]. While we accept that there were no deaths directly attributable to radiation, it is surprising that only 53 per cent of patients were alive at 1 year. We would be interested to know the cause of death in the 20 patients (47 per cent) who died within 12 months. Although the comments with respect to toxicity scoring systems are valid for late toxicity, in this study, examining acute toxicity, we have reported stochastic events. We would also be most interested to know the evidence for their statement that patients who are downstaged from node positive to node negative tend to have a worse outlook than genuinely node-negative patients.

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Pancreas and Islet Transplantation

N. Hakim, R. Stratta and D. Gray (eds)

170 × 245 mm. Pp 378 2002 Oxford: Oxford University Press £75·00.

This book aims to give an authoritative account of pancreas transplantation. It is prompted by pancreas transplantation becoming a recognized treatment option for diabetes and the treatment of choice for diabetic uraemic patients. The book is edited by three surgeons who have considerable experience in this field and contains contributions from 35 individuals who are mainly based in the USA and Europe. The chapter authors include some pioneers of pancreas transplantation. The text is generally well written, with adequate up-to-date references, and covers all aspects of historical background, indications for transplantation, organ procurement, surgical techniques and perioperative care. It also covers newer approaches, including islet cell transplantation, gene therapy and fetal tissue transplantation. There is some repetition in the text and the book would have benefited by additional illustrations and colour histograms. The work appears to be aimed at senior surgical trainees with an interest in transplantation, but it would also be of interest and a useful reference source for all those involved in the management of diabetic patients.

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Surgical Treatment of Haemorrhoids

C. V. Mann (ed.)

195 × 275 mm Pp 178 Illustrated. 2002. Heidelberg. Springer £75 00

A textbook dedicated entirely to the treatment of haemorrhoids has been lacking and much needed, not only because of the high prevalence of the disease but (especially) because of the great proliferation of surgical and non-surgical treatments proposed in recent years; these have caused confusion and uncertainty for both patients and surgeons. This book, written by Charles V. Mann in collaboration with 22 acknowledged experts in the field, includes chapters on the history of haemorrhoids, anatomical aspects and pathophysiology, diagnosis, and indications for treatment. Other chapters deal with surgical and non-surgical treatments of haemorrhoids, including some obsolete or abandoned techniques, such as Lord's procedure, cryotherapy, laser haemorrhoidectomy and Parks' method. Each chapter has an editorial comment followed by references and suggestions for further reading. Other aspects considered are complications and their management and the final chapter focuses on day-case haemorrhoidectomy, which nowadays is one of the targets of the health services in most European countries.

The text dealing with techniques features some good schematic diagrams and a few black and white photographs, but something more might have been expected from a textbook on this topic published in 2002. The chapter devoted to stapled haemorrhoidectomy (called anopexy) should have included documentation of the results of several randomized controlled trials published in 2001 which addressed all the uncertainties noted by the editor in his comment. Furthermore, new ways of performing the Milligan–Morgan operation, using ultrasonography or radiofrequency scissors, that have been claimed to be less painful than the original operation, should have been mentioned. Finally, among the non-surgical treatments, Doppler terminal rectal artery ligation has recently been attempted with promising results. In conclusion, in view of the rapid evolution of technology in the treatment of haemorrhoids, this book will require a new updated edition as soon as possible.

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The Diabetic Foot: Medical and Surgical Management

A. Veves, J. M. Giurini and F. W. LoGerfo (eds)

255 × 180 mm Pp 474 Illustrated. 2002 Totowa, New Jersey. Humana Press $145 00

This book is a worthy effort at covering all aspects of the diabetic foot in one text. The opening chapter is an excellent general account of diabetes and is followed by chapters on every aspect of the diabetic foot, including pathophysiology, biomechanics, bacteriology, diagnostics and all treatment methods. Of specific interest to the surgeon are the chapters on local surgery for sepsis and those on orthopaedic, plastic, vascular and radiological procedures. Recent advances in dressings and other local wound treatments are also discussed.

The chapters are written by many different authors and vary somewhat in style. Some reflect the author's individual views, occasionally to a more than ideal extent, but the great majority are very readable, supply the relevant information and are comprehensively referenced. The chapter on epidemiology is disappointingly indigestible, while that on diabetic neuropathies is particularly well written and informative. There are a surprising number of typographical errors and some of the introductions to the chapters overlap with each other in content with some conflict in detail. In summary, this is a competent text on the diabetic foot in which the specialist will find sufficient detail of significant value, as well as comprehensive background information.

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Thoracic Surgery. 2nd ed.

F. G. Pearson, J. D. Cooper, J. Deslauriers, R. J. Ginsberg, C. A. Hiebert, G. A. Patterson and H. C. Urschel Jr (eds)

220 × 285 mm. Pp. 1942. Illustrated. 2002. Edinburgh: Churchill Livingstone. £185·00.

Thoracic disease (which in this book excludes both heart and oesophagus) requires surgical input in diagnosis and management across a range of pathologies and a large repertoire of procedures; these are covered comprehensively. There is uncertainty about the future of British thoracic surgical practice: in England and Wales there are only 30 thoracic surgeons. In many parts of Europe thoracic surgery is part of a visceral surgeon's work. This model is seen by some as the way ahead for the UK where, at present, the majority of pulmonary and pleural procedures are performed by cardiothoracic surgeons in addition to their busy cardiac workload. Pulmonary disease is common, patients sit in medical wards with pleural problems unresolved, and the lung is now the commonest site for cancer. Whoever is to cope with the future care of these patients, whether it be cardiac surgeons with mixed practice, a new generation of thoracic specialists, or general surgeons, they will need a solid source of well indexed information and they will find it in this book. Inevitably I disagree on some details, but the editors have foreseen this and selectively added 'comments and controversies' at the end of each chapter, in an interesting approach that puts the more idiosyncratic or outmoded opinions into contemporary context.

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Recent Advances in Surgery 25

C. Johnson and I. Taylor (eds)

230 × 155 mm. Pp. 229. Illustrated. 2002. London: Royal Society of Medicine Press. £32·95.

This is an interesting book which focuses on novelties in general surgery. It is, of course, impossible to cover all the new and interesting data available, but the authors have tackled specific topics and provided a short review of each. The choosing of topics can always be discussed but, as this is a yearbook, most areas in general surgery are likely to be covered within any 5-year period. I particularly appreciated the final chapter on randomized trials. It is important that clinical research around the world is carried out within randomized trials and so this particular chapter is of the utmost importance, not only to provide results but also to highlight the whole concept of randomized trials.

There is always a problem with books like this that have several authors. The quality of chapters differs, as does the way different areas are covered. It is also easy to cite articles and papers which fit the author's own preference and so bias the chapter. This will always be a minor drawback to books like this but, as a brief review of what is going on in general surgery, I think it is otherwise ideal. This is not a book for the subspecialist but merely a review for those surgeons who want to be informed about what is happening. It could be recommended as a book for the departmental library.

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Principles and Practice of Surgery. 4th ed.

O. J. Garden, A. W. Bradbury and J. Forsythe (eds)

190 × 245 mm. Pp. 632. Illustrated. 2002. Edinburgh: Churchill Livingstone. £35·95.

The authors have built on the success of the previous editions of this work to produce a high-quality undergraduate medical textbook which is easy to read. The illustrations are of high quality and so have a good visual impact. The use of summary boxes at the end of each topic aids revision, and these are uncomplicated and effective. The paediatric icons that are used throughout the text are also a welcome addition. Overall, the book is thorough, accurate, and would be suitable as an undergraduate textbook. It can also be used both as a general reference work and as an aid to basic surgical training. In addition, the pathophysiology included in this edition gives a good grounding and would supplement a core curriculum in preparation for the Membership of the Royal College of Surgeons examination. Overall the authors have done very well.

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Scientific Surgery

Lindsey I, George B, Kettlewell M, Mortensen N. Randomized, double-blind, placebo–controlled trial of sildenafil (Viagra) for erectile dysfunction after rectal excision for cancer and inflammatory bowel disease. *Dis Colon Rectum* 2002; **45:** 727–32.

This blinded crossover trial included 32 patients with impotence after undergoing rectal excision. There was improvement in 79 per cent of patients with sildenafil, significantly more than with placebo (*P* = 0·0009).

Phillips RKS, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP *et al.* A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50:** 857–60.

Some 83 subjects were included in a study of two different dose schedules. The higher dose (400 mg b.d.) of celecoxib reduced the number of areas involved with polyps by 14·5 per cent (*P* = 0·43); the effect was greater in patients with clinically significant disease at baseline.

Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D *et al.* Intranasal mupirocin to prevent post-operative *Staphylococcus aureus* infections. *N Engl J Med* 2002, **346:** 1871–7.

Over 4000 patients undergoing general, gynaecological, neurosurgical or cardiac procedures were enrolled. Mupirocin did not reduce the overall rate of surgical site infections, but in the 891 patients with *Staphylococcus aureus* in their nose preoperatively, the rate of infection was reduced from 7·7 to 4 per cent, *P* = 0·02.

Coccheri S, Scondotto G, Agnelli G, Aloisi D, Palazzini E, Zamboni V for the SUAVIS Group. Randomised, double blind, multicentre, placebo controlled study of sulodexide in the treatment of venous leg ulcers. *Thromb Haemost* 2002; **87:** 947–52.

Some 235 patients were included and treated with standard wound care and compression bandaging. Sulodexide was well tolerated and improved both 2- and 3-month ulcer healing rates (*P* = 0·018 at 2 months) compared with placebo.

Lederman RJ, Mendelsohn FO, Anderson RD, Saucedo JF, Tenaglia AN, Hermiller JB *et al.* Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. *Lancet* 2002; **359:** 2053–8.

Some 190 patients were randomly allocated to one or two intra-arterial injections of fibroblast growth factor-2 at 1-month intervals, or placebo. A single dose of fibroblast growth factor-2 increased 90-day peak walking time by 1·77 min, compared with 0·6 min for placebo (*P* = 0·034 on intention to treat). The second dose did not appear to improve this effect.

The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen *versus* tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359:** 2131–9.

A total of 9366 women were included with a median follow-up of 33·3 months. Disease-free survival at 3 years was 89·4 per cent for anastrozole alone and 87·4 per cent for tamoxifen alone (*P* = 0·013). Results for the combination were similar to tamoxifen alone. The benefit was only seen in oestrogen receptor-positive tumours. There were more side-effects with tamoxifen.

Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002; **50:** 840–4.

These are late (11 years) results from a screening trial including 152 850 participants. There was a 13 per cent reduction in colorectal cancer mortality despite an uptake of only 60 per cent. The reduction in mortality was 27 per cent in those actually screened.

Chung CC, Ha JPY, Tai YP, Tsang WWC, Li MKW. Double-blind, randomized trial comparing harmonic scalpel haemorrhoidectomy, bipolar scissors haemorrhoidectomy, and scissors excision. *Dis Colon Rectum* 2002; **45:** 789–94.

Eighty-six patients were randomized and followed up at 4 and 12 weeks after surgery. Harmonic scalpel excision had least blood loss and best satisfaction scores, but clinically measured outcomes and complications were similar between the groups.

Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C *et al.* Effect of therapeutic footwear on foot reulceration in patients with diabetes. *JAMA* 2002; **287:** 2552–8.

Four hundred patients with diabetes were randomly allocated to one of three trial groups. Neither of the therapeutic shoe or insert groups had a reduction in the rate of re-ulceration after 2 years (15 per cent overall).

Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359:** 1812–18.

Twenty patients were studied: ten received normal postoperative intravenous fluids and ten had restricted intake of salt and water. Return of gastrointestinal function was quicker in patients who were restricted; they had fewer complications (one *versus* seven, *P* = 0·01) and left hospital sooner (median 6 *versus* 9 days, *P* = 0·001).

The *BJS* website can be found at *www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Instructions to authors

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Disks

IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors. Proofs will be sent via e-mail as an Acrobat portable document format (PDF) file.

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BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

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Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; **354**: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

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On the title page give: (1) the title of the article; (2) the name and initials of each author, (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed**; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc)

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This must not exceed 200 words and should be presented in a structured format **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted

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Submit four copies of all illustrations and tables Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s), indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (www.consort-statement.org).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to three decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

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